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rescribing information
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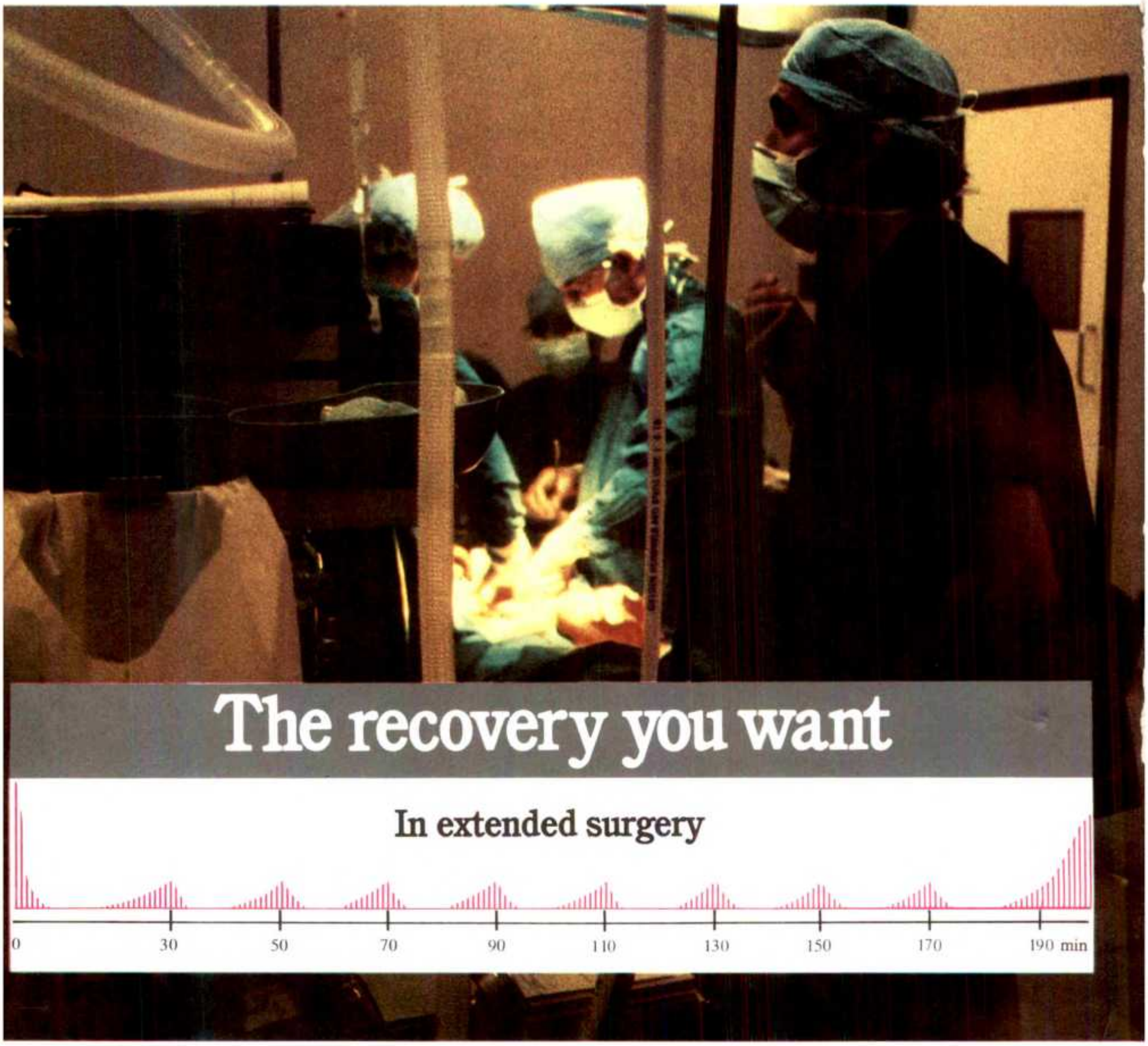

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1. Data on file, Wellcome, 1987.
2. Yate, P.M. *et al.* (1986), *Br. J. Anaesth.*, **58**, 112 S.

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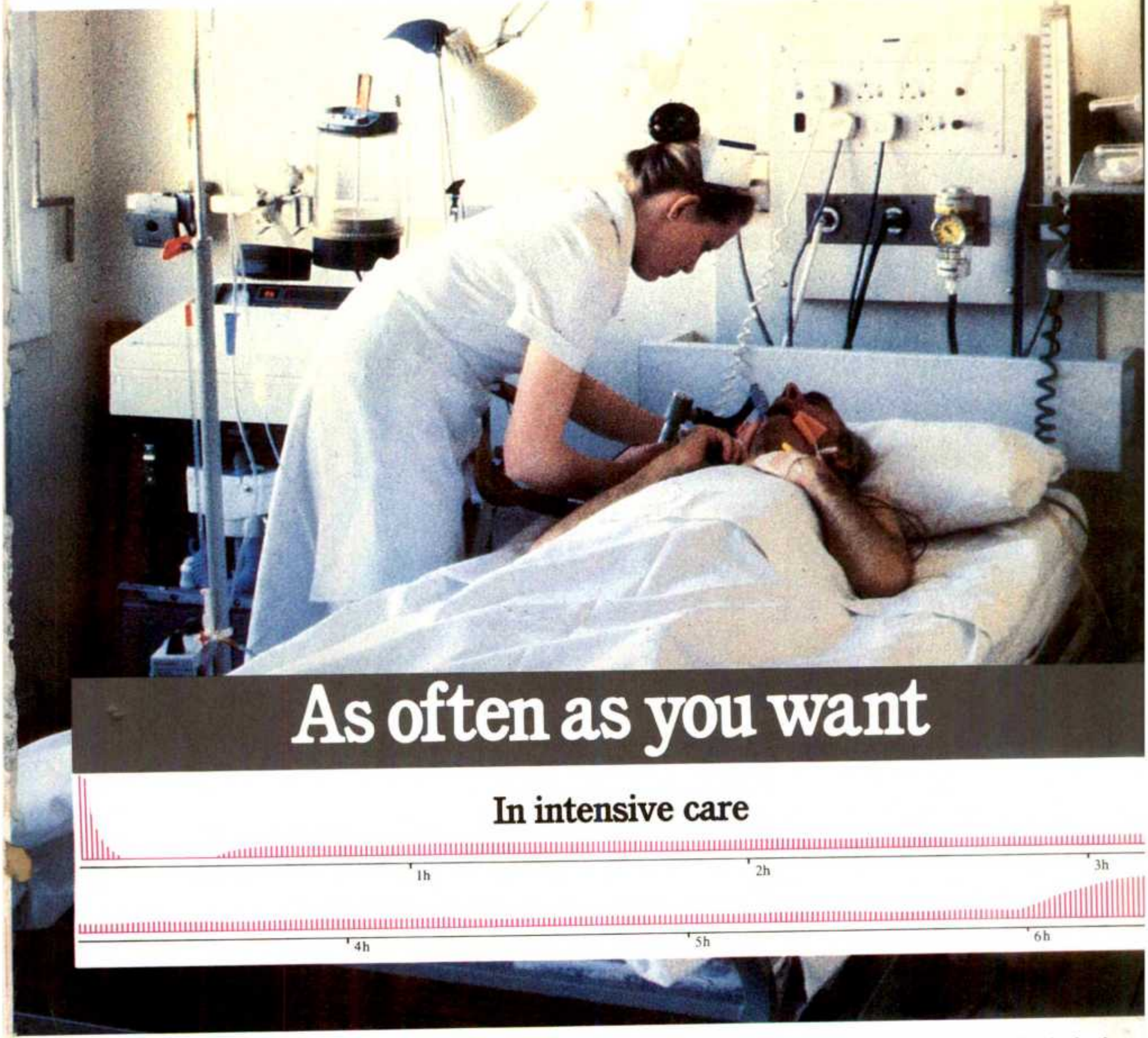

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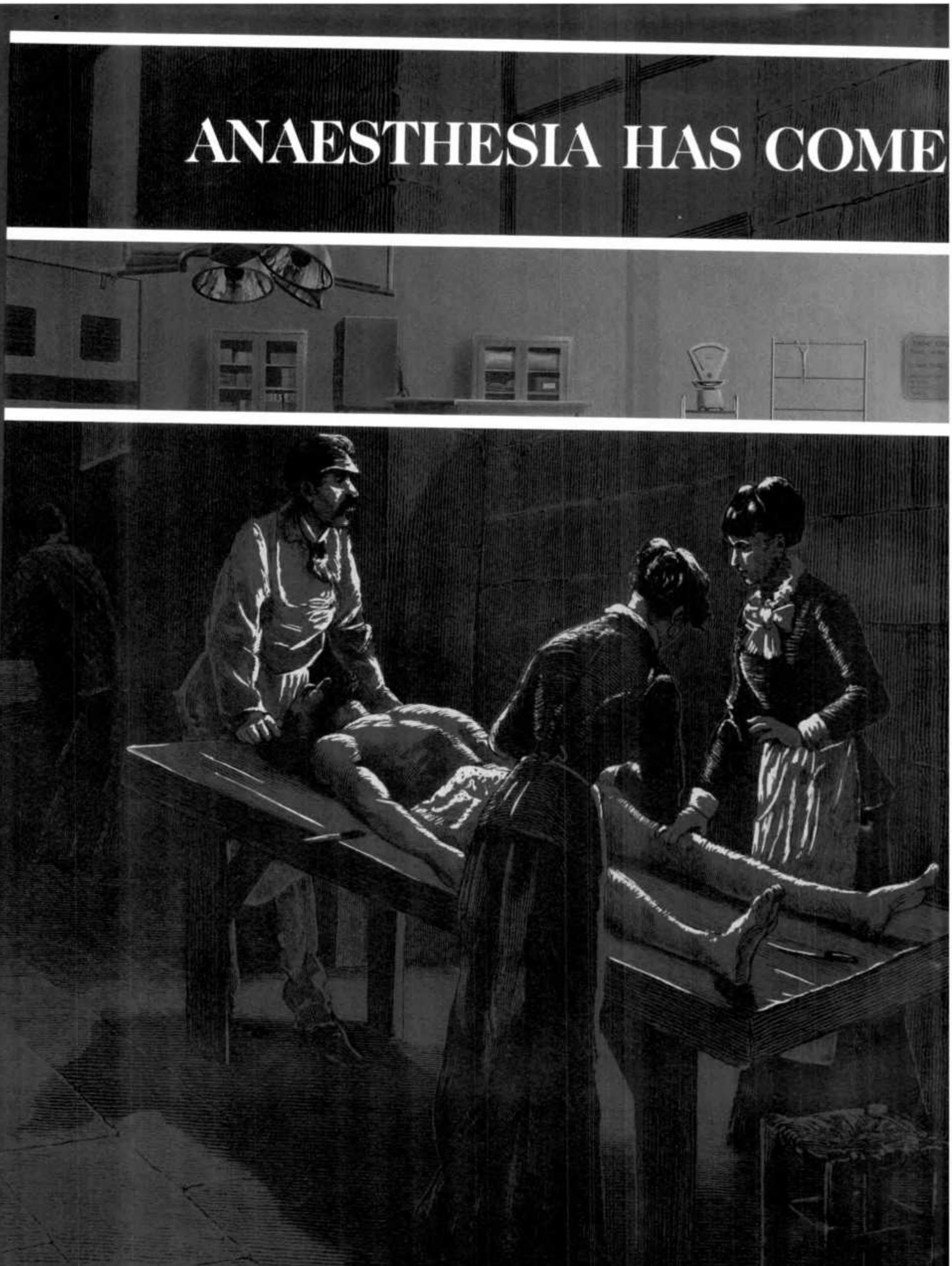

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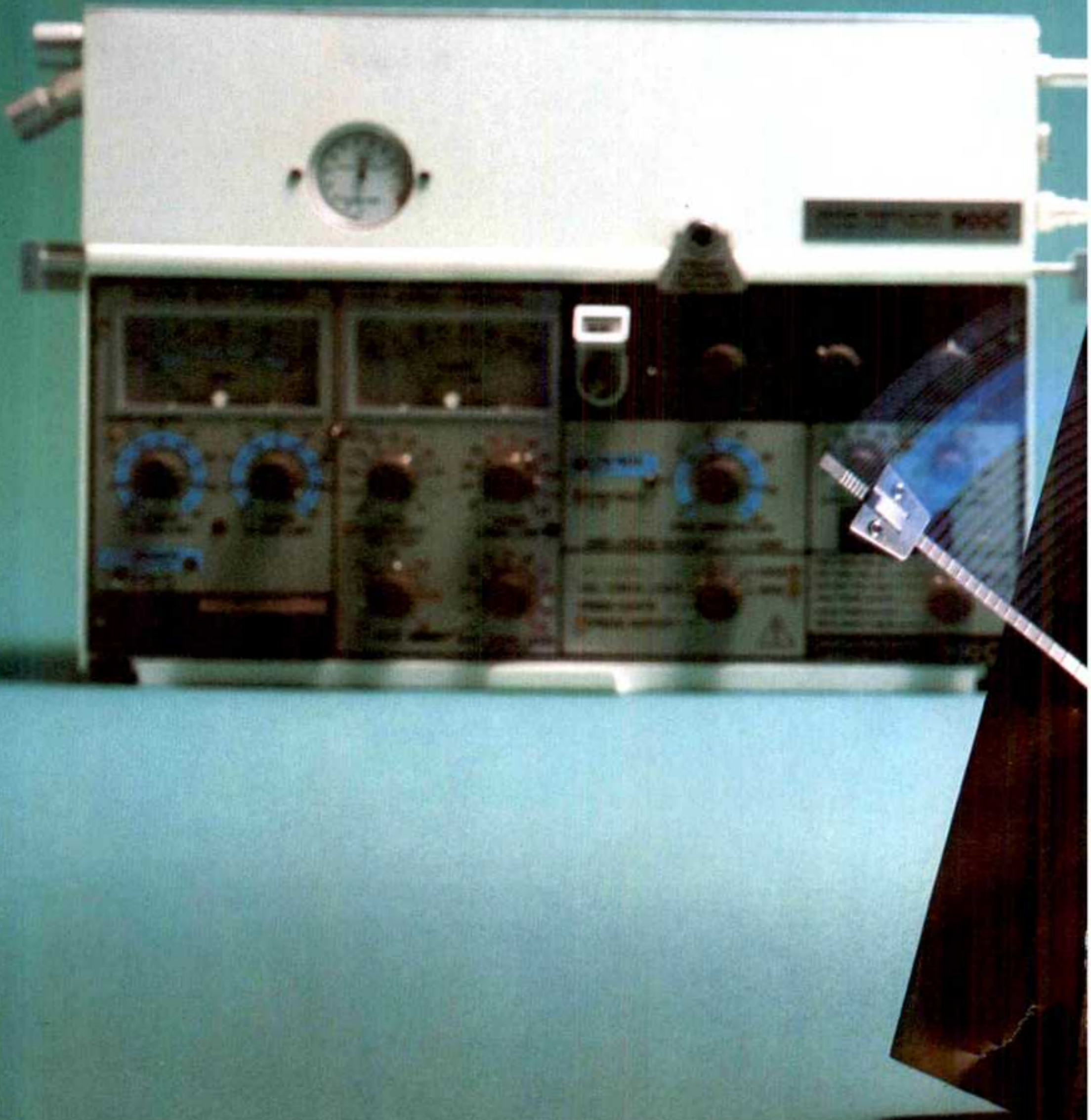

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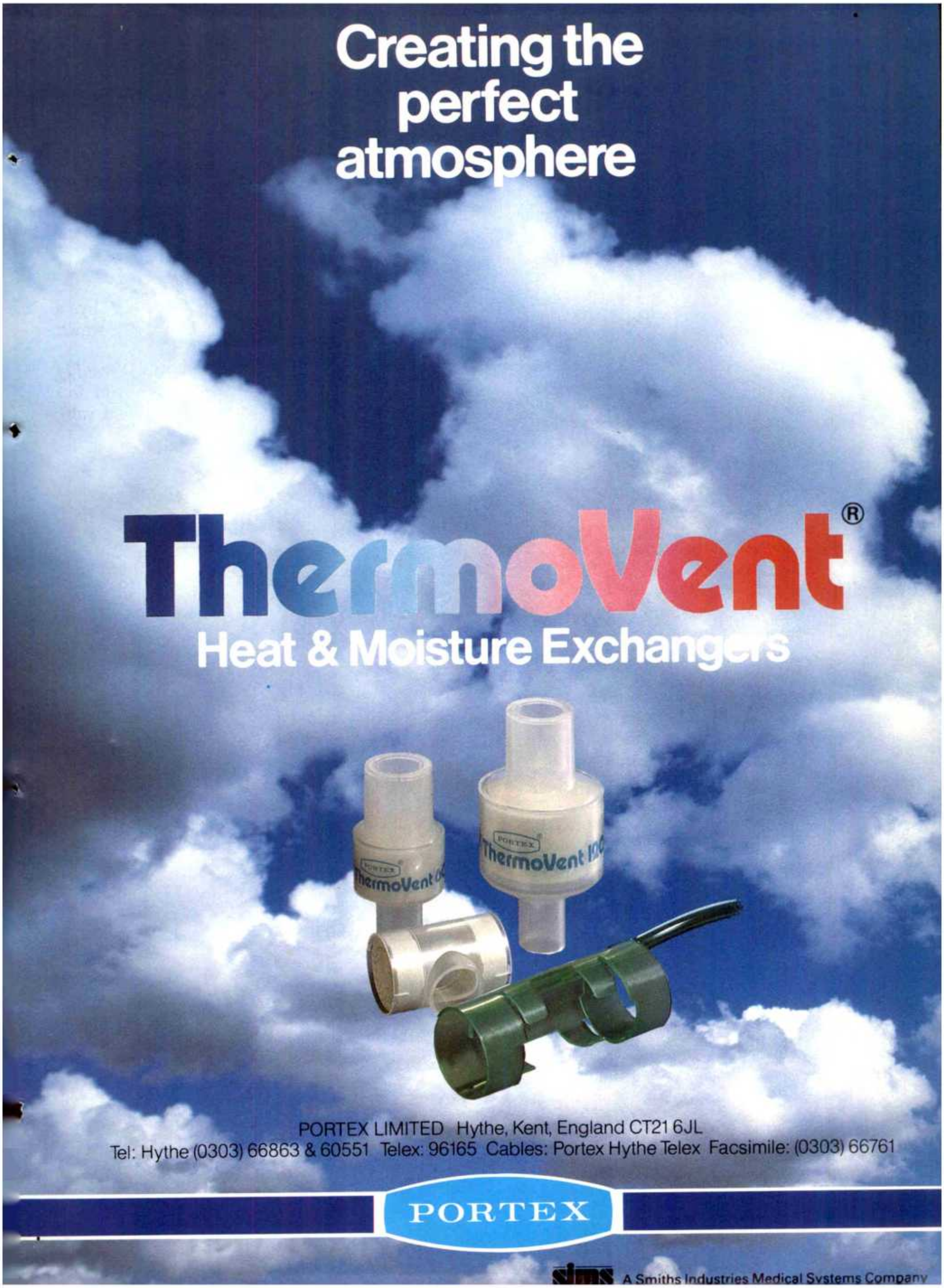

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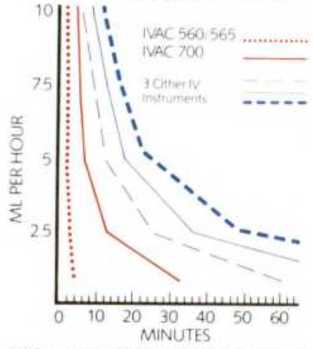

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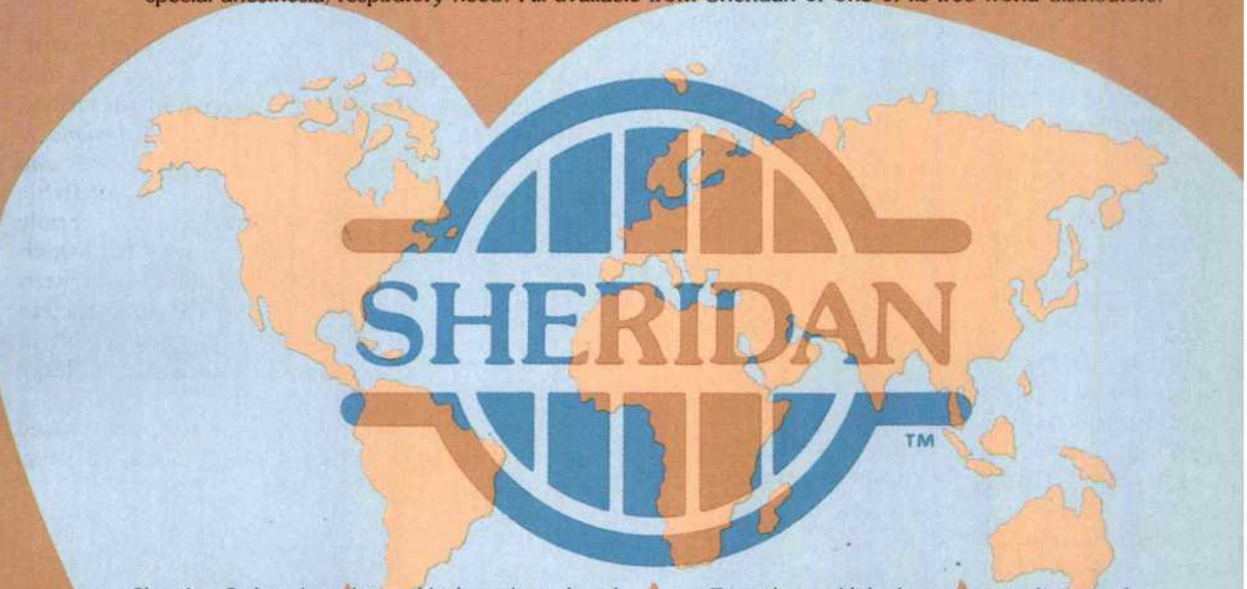

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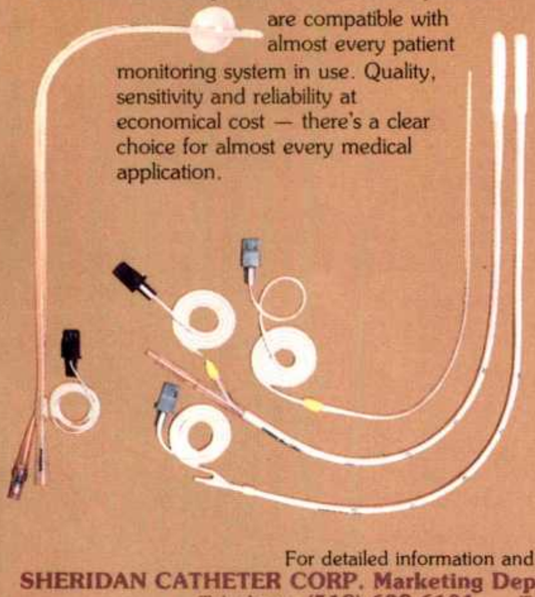

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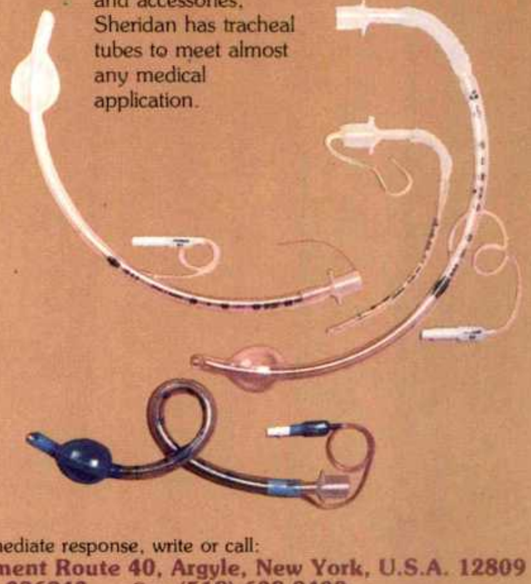

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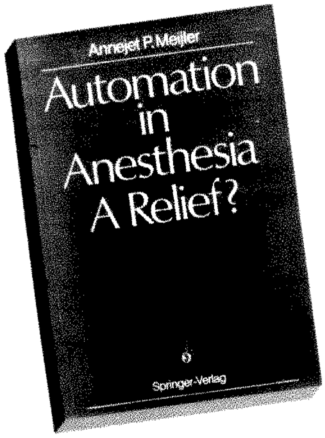

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M. P. B. Halmágyi, University of Mainz

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Pulmonary Function Indices in Critical Care Patients

1987. Approx. 130 pages.
Soft cover DM 98,–. ISBN 3-540-18432-5

In this volume, physicians and engineers combine forces to tackle the questions of how to measure functional residual capacity in the intensive care patient. The following topics are discussed: clinically important pulmonary function index, principles of model development for spontaneous respiration and mechanical ventilation, assessment of pulmonary function indices, cases to prove the measuring system, standard lung function indices, effect of isolated changes in breathing pattern compared by various steady states, and intermittent mandatory ventilation (IMV). Appendices are attached for a better understanding of the physiological and mathematical background.

J.-L. Vincent, Free University of Brussels;
L. G. Thijs, University of Amsterdam (Eds.)

Septic Shock

European View

1987. 76 figures, 50 tables. IX, 291 pages.
(Update in Intensive Care and Emergency Medicine, Volume 4).
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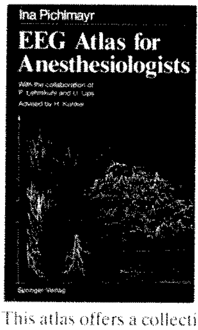

1987. 202 figures.
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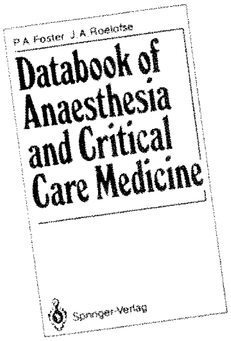
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London (Eds.)

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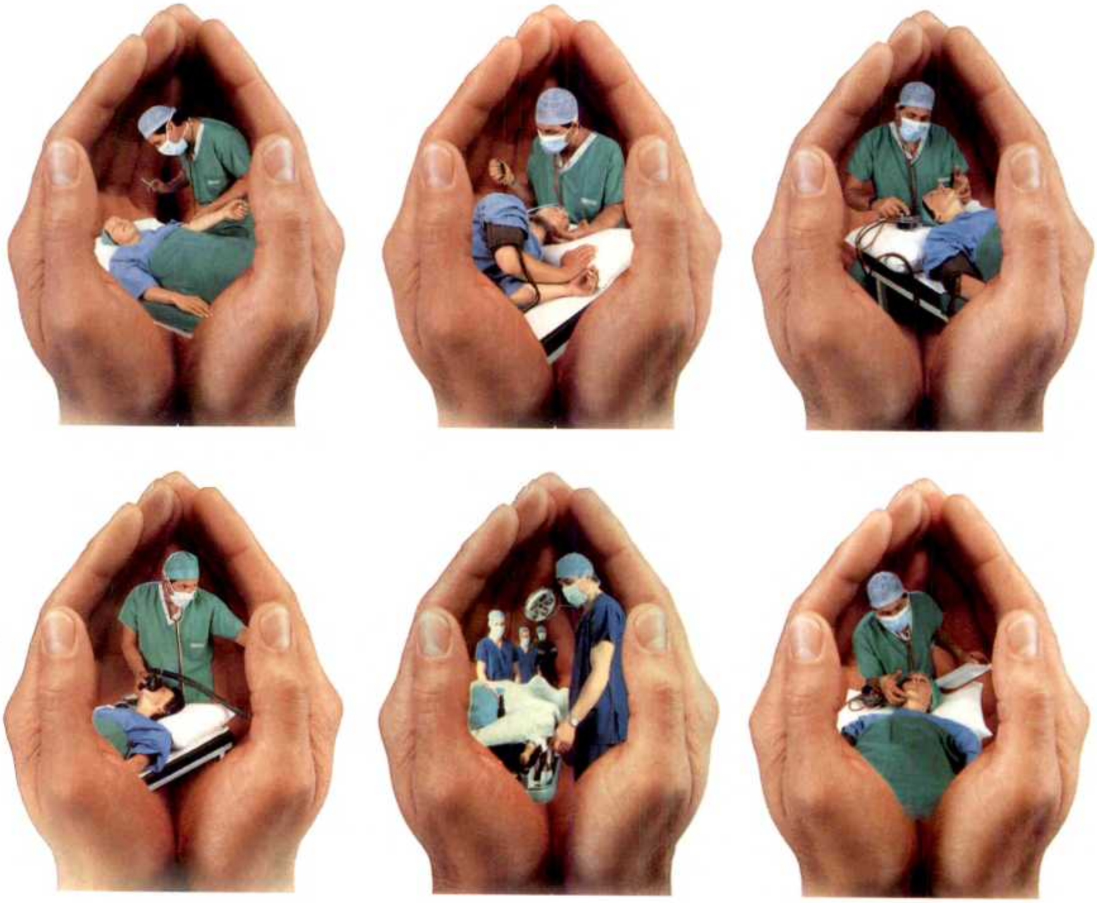

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 60, No. 5 APRIL 1988

EDITORIAL

NEW NON-INVASIVE METHODS FOR MEASURING GASTRIC EMPTYING

The physiological, pathological and pharmacological factors which affect the rate of gastric emptying impinge on anaesthetic practice in a number of ways. Inhalation of gastric contents may be a major cause of morbidity and mortality. Nausea and vomiting are distressing sequelae of anaesthesia. Changes in gastric emptying have important effects on the absorption of orally administered drugs, including premedicant, analgesic and concurrent medication. Improved understanding of these factors depends upon techniques for the practical measurement of gastric emptying. Although a number of methods have been developed, so far none is ideal (that is safe, non-invasive, non-radioactive, applicable to solid or liquid test meals and repeatable).

Scintigraphy using a radiolabelled test meal and a gamma camera is non-invasive, but the use of radioactive isotopes precludes repeated studies in the same patient, and during pregnancy. Gamma cameras are expensive and not readily available for routine clinical or experimental purposes. The images may be subject to errors caused by changes in distance between isotope and camera as the stomach empties as a result of both the inverse square law and tissue attenuation.

Marker dilution is accurate and repeatable, but gastric intubation is unpleasant and may itself affect gastric motility through both mechanical and psychological effects. It is applicable only to liquids and the repeated mixing and aspiration of gastric contents provides a limited number of data points.

Absorption of paracetamol after its administration by mouth is an index of gastric emptying as this drug is absorbed only after it has left the stomach. The technique has been used to demonstrate delayed gastric emptying following opioid analgesia during labour [1] and to demonstrate the intestinal prokinetic action of cisapride after morphine premedication [2]. However, it requires repeated blood samples and is only an indirect measure.

Real-time ultrasound is non-invasive and safe and has been used to measure gastric emptying in volunteers [3]. A series of cross-sectional scans along the long axis of the stomach is obtained and the volume computed using a video cassette recorder and a microcomputer. The accuracy of the method was assessed by scanning balloons filled with known volumes of water: in the hands of an experienced operator the mean error of the computed volumes was 4%. Gastric emptying after a 500-ml orange drink was measured in volunteers and found to be log-linear; the half-life of emptying was reduced in four of the five subjects by i.v. metoclopramide given 10 min before. The method seems to fulfil many of the criteria for an ideal technique, disadvantages being the size and the relative expense of the ultrasound scanner and ancillary equipment and the need for an experienced operator.

The measurement of electrical impedance can provide the basis for measuring gastric emptying if the test meal has electrical conductivity different from that of surrounding tissues. Two techniques have been described recently and offer considerable advantages over the more invasive methods [4–6].

Measurement of epigastric impedance is the simpler technique. Two adhesive electrodes are placed in standard positions on the front of the abdomen and two on the subject's back. A constant 2-mA 100-kHz current is passed across the abdomen through one pair of electrodes and the potential difference measured between the second pair. The output signal is displayed on a chart recorder. The maximum deflection of the trace after drinking a test meal is designated 100% and the time taken to reduce to 50% (or any other fraction) of the original deflection is measured.

Epigastric impedance has been used to measure gastric emptying in a simultaneous comparison with scintigraphy [4]. There was a significant correlation between the slopes of the declination curves measured by the two methods in six healthy volunteers. The technique has also been shown to give results in accord with simultaneous dye dilution measurements and has demonstrated a faster rate of emptying after i.v. metoclopramide in volunteers [5]. Epigastric impedance used to measure gastric emptying after 500 ml of water or orange drink in obstetric patients demonstrated delayed emptying in the first 1 h after delivery following opioid analgesia during labour. Gastric emptying in women in the third trimester of pregnancy was not different from that in women who were not pregnant.

One major problem encountered was inability to locate the stomach in 14 of the 68 women studied, and this included 10 of the 30 in the third trimester. This was attributed to displacement of the stomach in a manner similar to the rostral rotation of the stomach which occurs in obese subjects. Other problems encountered were vomiting of the test meal by two of the post-partum group and artefact caused by excessive movement in a further two subjects.

A further and more serious difficulty is the relationship between epigastric impedance and the contents of the stomach. Although the decline in the initial deflection of the trace is clearly related to the rate of gastric emptying, the assumed linear relation between the volume of gastric contents and the change in impedance has not been demonstrated. A related problem is the effect of gastric acid on the measured impedance. Repeated aspiration of small volumes during a 20-min period following the ingestion of 600 ml of orange drink showed that pH decreased progressively and the conductivity increased, despite the absence of protein or fat which stimulate the cephalic phase of gastrin-mediated gastric secretion [5]. Impedance is clearly related to the conductivity of the gastric contents and the effect of acid secretion is to increase the apparent rate of emptying indicated by impedance measurements. This is supported by simultaneous comparison of scintigraphy and epigastric impedance: the gastric half-emptying time obtained by the impedance technique was faster than that obtained by scintigraphy in all six subjects [4]. Perhaps an H2-antagonist should be administered before epigastric impedance tests. The relation between volume of gastric contents and the measured impedance has yet to be clarified.

The second technique based on detecting changes in resistivity is that of applied potential tomography (APT), which creates cross-sectional images of the body based on tissue resistivity. The name APT invites comparison with x-ray computed tomography (CT), but the analogy is not an exact one. The images from CT scans are derived from collimated beams of x-rays which are absorbed to a variable extent, whereas the current in APT follows the path of least electrical resistance. Laplace's law describes the voltage distribution within a body as a function of position and conductivity and the problem in impedance imaging is to determine the spatial distribution of resistivity from the measured surface potentials. This inverse solution to Laplace's equation is a complex mathematical problem, but a working device capable of generating images of tissue resistivity is now available [6]. Sixteen electrodes are placed in a ring around the upper abdomen at the level of the stomach. An alternating current of 1 mA at 50 kHz is passed between two adjacent electrodes and the potential differences between the other 13 adjacent electrodes are measured. The process is repeated using each pair of electrodes in turn as the drive electrodes. A computer generates a tomographic image from data from 150 cycles, collected over approximately 30 s to reduce the effect of respiratory movements. Following ingestion of a solid or liquid test meal, the position of the stomach can be outlined using a cursor on the computer-generated image and the change in resistivity within this area is calculated for each subsequent image to yield a profile of gastric emptying. Although the spatial resolution is poorer than CT, with a spatial resolution of approximately 10% of the field diameter, the sensitivity to changes in resistivity is very good: 1% changes can be detected.

A recent study has described the use of APT to measure gastric emptying [7]. The optimum position of the electrodes was determined using scintigraphy: positioning of the electrodes at the level of the eighth costal cartilage was found to coincide with the level of the body or fundus of the stomach in all 19 subjects examined. A linear relationship was demonstrated between the volume of an intragastric balloon and the APT value up to a volume of 250 ml. The effect of acid secretion was examined by two methods: first, by stimulating secretion with subcutaneous pentagastrin and second, by measuring gastric emptying with and without the prior administration of cimetidine. Acid secretion increased the gastric conductivity as expected and, whereas there was a strong correlation between the gastric half-emptying times obtained in repeated studies on each subject after cimetidine, there was no correlation between the half-emptying times in repeated studies when acid secretion was not inhibited. Cimetidine itself does not affect gastric emptying [8, 9]. APT was compared in simultaneous studies of emptying of liquid meals (with both scintigraphy and dye dilution) and of solid meals (with scintigraphy): in all cases there was good correlation between the gastric half-emptying times obtained with APT and the other methods. Test meals were used which were either more or less conducting than the surrounding tissues and were found to give equally good results.

APT clearly has considerable potential for measuring gastric emptying in a clinical setting. However, unlike ultrasound and epigastric impedance, it has been used only in healthy volunteers. Nevertheless, the availability of techniques for measuring gastric emptying which are non-invasive, non-radioactive, relatively portable and repeatable should provide a stimulus to further research in this important subject.

D. A. J. Walker and W. S. Nimmo

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Br. J. Anaesth. (1988), **60**, 486–490

FADE PROFILES DURING SPONTANEOUS OFFSET OF NEUROMUSCULAR BLOCKADE: VECURONIUM AND GALLAMINE COMPARED

S. J. POWER, A. C. PEARCE AND R. M. JONES

SUMMARY

The characteristics of the train-of-four (TOF) response have been studied electromyographically during the onset and the spontaneous offset of neuromuscular blockade inducd with vecuronium or gallamine. During the onset of blockade, at 75% depression of initial twitch height, gallamine was associated with significantly more TOF fade than vecuronium. Both agents were associated with significantly less fade during onset than during spontaneous offset. When the two neuromuscular blocking drugs were compared during spontaneous offset they showed a similar degree of fade during early offset (up to 50% recovery of initial twitch height). However, during late spontaneous offset, when the initial twitch height had recovered to 75% of control values, vecuronium was associated with more fade than gallamine.

It has been noted that different neuromuscular blocking drugs are associated with varying degrees of fade when neuromuscular block is monitored with repetitive or high frequency stimulation (such as train-of-four (TOF) or tetanic stimulation). The majority of previous studies have observed and reported the degree of fade during the onset of blockade [1,2]. The characteristic "fade profiles" of individual myoneural blockers have been ascribed to their varying affinities for pre- and postsynaptic receptors [1,3] and has led to the suggestion that neuromuscular blocking drugs and their antagonists may be matched in terms of their pre- and postsynaptic activity [4].

However, the degree of fade occurring during the onset of blockade may not be the same as during offset [3,5–7], when antagonists are administered. We have studied the degree of TOF fade during spontaneous offset, as well as onset, for gallamine and vecuronium—agents which are thought to have widely varying degrees of pre- and postsynaptic activity [1–3,8].

PATIENTS AND METHODS

After local ethics committee aproval, 30 patients (ASA class I and II) scheduled to undergo elective surgery requiring the use of neuromuscular blocking drugs gave their informed consent to inclusion in this study. All patients were within 20% of their ideal weight. Patients with neuromuscular, hepatic or renal disease were excluded, as were any patients receiving medications known to influence neuromuscular transmission. The non-dominant arm was immobilized in a splint and used for electromyographic monitoring (Datex Relaxograph) utilizing the ulnar nerve at the wrist and the hypothenar muscles for positioning of the stimulating and recording electrodes. A TOF pattern of stimulation with supramaximal 0.1-ms square wave impulses was used, and repeated every 20 s.

A standardized, but not randomized, anaesthetic technique was used. Patients were either unpremedicated or they received diazepam 10 mg by mouth approximately 1 h before operation. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} after fentanyl 1 µg kg^{-1} had been injected through an indwelling needle to a vein on the dorsum of the dominant hand. The patient spontaneously breathed 66% nitrous oxide in

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S. J. POWER, M.B., B.S., F.F.A.R.C.S.; A. C. PEARCE, M.B., B.CHIR., M.R.C.P., F.F.A.R.C.S.; R. M. JONES, M.B., CH.B., F.F.A.R.C.S.; United Medical & Dental Schools, University of London, Department of Anaesthetics, Guy's Hospital, London Bridge SE1. Accepted for Publication: December 19, 1986.

oxygen with 1 % inspired halothane delivered via a Bain type coaxial breathing system and facemask. Baseline neuromuscular recordings were obtained and when they were stable, approximately equipotent doses (ED_{95}), of either vecuronium (0.05 mg kg^{-1}) or gallamine (2.0 mg kg^{-1}) were injected through the same needle, preceded and flushed with 1 ml of physiological saline. The neuromuscular blocking drugs were injected at the same rate, as a rapid bolus. Tracheal intubation was performed when the first twitch of the train (T1) was 5 % of control or after 4 min, whichever was sooner. Anaesthesia was maintained with 66 % nitrous oxide and 0.5 % inspired halothane in oxygen plus incremental doses of fentanyl as indicated. Intermittent positive pressure ventilation utilized a Nuffield 200 series anaesthesia ventilator and Bain type circuit with fresh gas flow of 70 ml kg^{-1} min^{-1}.

A complete record of twitch height was obtained during onset, spontaneous offset and after the administration of the anticholinesterase. Two indices of neuromuscular blockade were recorded: the height of T1 compared with control T1 (T1 : control %) and the ratio of the height of the fourth to the height of the first response in the same train (T4 ratio). The records were judged to be suitable for analysis if T1 following evoked reversal was 90–110 % of control T1. Comparisons of fade between drugs were made at the T1 value nearest to 25 % of control (T1 : control 25 %) during onset and at 25, 50 and 75 % of control (T1 : control 25, 50 and 75 %) during spontaneous offset.

The results are expressed as mean (± SD). Statistical analysis utilized non-parametric methods (Wilcoxon's rank sum test or Wilcoxon's signed rank test), as appropriate.

RESULTS

Although 30 patients were studied, the records for only 11 patients receiving vecuronium and eight patients receiving gallamine were suitable for analysis based on the described criterion. The demographic data are shown in table I.

TABLE I. *Demographic data of the patients*

		Vecuronium	Gallamine
n		11	8
Sex (M/F)		5/6	4/4
Age (yr)	mean (SD)	30(14)	53(18)
	median	26	52
	range	19–70	25–75
Weight (kg)	mean (SD)	64(9)	69(9)
	median	68	71
	range	52–75	53–80

During the onset of neuromuscular blockade, at T1 : control 25 %, the T4 ratio was 0.47 (0.09) in the vecuronium group and 0.13 (0.11) in the gallamine group (fig. 1). The degree of fade was significantly greater with gallamine than with vecuronium ($P < 0.01$).

The times to return to all chosen offset T1 : control values were much longer in the gallamine group: for example, T1 : control 50 % for gallamine was 98 (50) min compared with 18 (3) min for vecuronium.

Comparisons of fade at T1 : control 25 % during onset and spontaneous offset of neuromuscular blockade showed significantly ($P < 0.01$) more fade during offset than during onset with both vecuronium and gallamine. The T4 ratios for vecuronium (fig. 1) were 0.47 (0.09) during onset of blockade and 0.06 (0.09) during offset. The results for the gallamine group demonstrated a similar pattern, with a T4 ratio of 0.13 (0.11) during onset and 0.04 (0.06) during spontaneous offset.

When the T4 ratios were compared during early spontaneous offset at T1 : control 25 % and 50 %, there were no significant differences between the two myoneural blockers. The T4 ratio for the gallamine group at T1 : control 25 % was 0.04 (0.06) compared with 0.06 (0.09) for the vecuronium group. When T1 had returned to 50 % of control, the T4 ratio for the patients receiving gallamine was 0.13 (0.06) and 0.12 (0.07) for the patients receiving vecuronium. However, during late spontaneous offset, when T1 had returned to 75 % control (fig. 1), the use of gallamine was associated with significantly ($P < 0.05$) less fade, having a T4 ratio 0.33 (0.07) compared with a T4 ratio 0.21 (0.08) for vecuronium.

DISCUSSION

It has been suggested that non-depolarizing neuromuscular blocking drugs inhibit neuromuscular transmission by acting at a number of sites within the neuromuscular junction, not just at the classical postjunctional nicotinic acetylcholine receptor [9–15]. It has also been suggested that fade occurring during the TOF or tetanus is

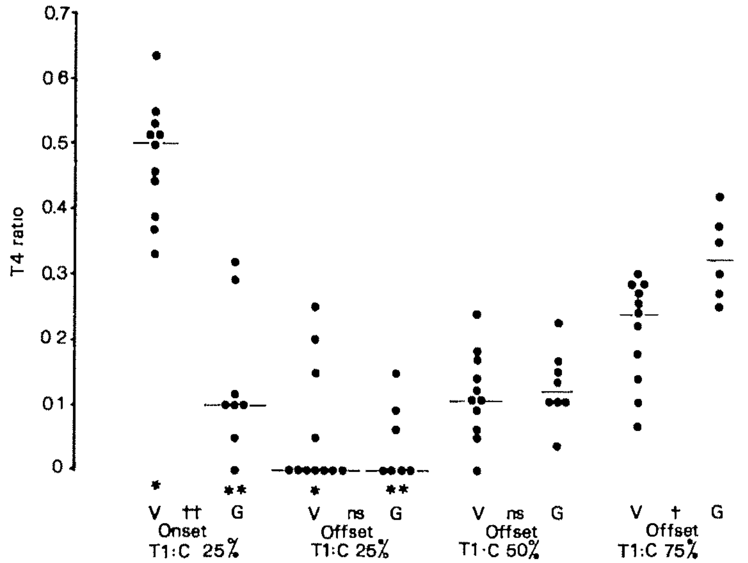

FIG. 1. T4 ratios for gallamine and vecuronium compared during the onset of neuromuscular blockade at T1:control 25% and during spontaneous offset at T1:control 25, 50 and 75%. Horizontal lines represent the median value for each group. Between-drug differences: †$P < 0.05$; ††$P < 0.01$; ns = not significant. *$P < 0.01$ for T4 ratios for vecuronium, compared at T1:control 25% during onset and offset. **$P < 0.01$ for T4 ratios for gallamine, compared at T1:control 25% during onset and offset.

one manifestation of the action of neuromuscular blockers at various sites within the neuromuscular junction. One explanation is that depression of the single twitch is explained by the action of the neuromuscular blocker at the postjunctional receptor, but that fade represents interaction with the prejunctional site.

Individual neuromuscular blocking drugs have been thought to have characteristic patterns of activity at the neuromuscular junction because of their varying affinity for pre- and postsynaptic sites and are thus associated with their own fade profile [1, 2, 8]. In this study we have investigated two neuromuscular blocking drugs thought to act at either end of the fade spectrum. Williams, Webb and Calvey [1] using electromyography, showed a marked degree of fade associated with the onset of blockade with gallamine, an observation which we confirmed. In contrast, vecuronium has been noted to be associated with less fade, when compared with pancuronium and gallamine during the onset of blockade [2]. Gallamine was associated with most fade, pancuronium with less and vecuronium with least fade. Indeed, it was suggested [2] that, because vecuronium was associated with so little fade, if lack of fade was used as the sole criterion for antagonism of blockade, patients could be left with significantly impaired muscle strength in the postoperative period. This work was performed on horses. Our study has confirmed previous findings in man and in terms of the degree of fade during the onset of gallamine- and vecuronium-induced block. (Gallamine showing a marked degree of fade during onset: at T1:control 25% the T4 ratio was 0.13 (0.11), compared with 0.47 (0.09) with vecuronium.)

Bowman [3] has demonstrated the variable relationship between the degree of fade during onset and offset, suggesting that the prejunctional receptors were isoreceptors of the postjunctional receptors with different pharmacological profiles. This explains the different affinities and rates of binding for the different myoneural blocking drugs. A slower rate of binding to these fade sites would explain the observation that depression of twitch and fade develop and recover with different time courses. He showed, in cats, the greater degree of fade during offset with vecuronium. These findings have been confirmed in man using vecuronium and atracurium [7]. Our present study confirms the findings of Pearce, Casson and Jones [7] with vecuronium, and shows that this is also true with gallamine.

However, when the two drugs are compared during spontaneous offset, as opposed to onset, we have demonstrated that they appear to have similar degrees of fade up to T1 : control 75% when the situation is reversed, with gallamine being associated with less fade than vecuronium.

Pearce, Casson and Jones [7] demonstrated that the degree of TOF fade during the onset of blockade depends upon the dose of myoneural blocking drug administered, with larger doses being associated with less fade. To exclude this effect in this study, we administered approximately equipotent (ED_{95}) doses—vecuronium 0.05 mg kg^{-1} and gallamine 2.0 mg kg^{-1}. As both drugs were administered on a weight-related basis, we included only patients within 20% of their ideal weight. The possible effects of cumulation resulting from an incremental technique were avoided in this study by administering only a bolus dose of neuromuscular blocking drug. For this reason we felt unable to randomize the administration of the chosen drug and gallamine was given for procedures which were anticipated to last for a minimum period of 1 h. There was thus a difference in the age of the two groups, with the gallamine group having a mean age 53 yr compared with 30 yr in the vecuronium group. Although the gallamine group were older, they were not elderly, and patients were included only if they had normal blood biochemistry suggesting no abnormality of excretion and presumably normal duration of action.

It should be noted that we utilized the integrated hypothenar electromyogram (as recorded by the Datex Relaxograph) and, although the results may not be strictly comparable with studies in which electro- or mechanomyography of the thenar muscles have been used, it is known that there is a good correlation between the different recording methods [16,17].

Results were included only if T1, after evoked reversal, returned to within 10% of control values. Thirty studies were performed, but only 19 achieved suitable results. In the 11 rejected recordings, T1 failed to reach 90% of control in nine and, in two, T1 increased to values greater than 110% after antagonism. Viby-Mogensen [18], in a review of the evoked electromyographic response, also noted that the response often did not return to 100% control during recovery. It is so far not known whether this is the result of technical problems such as changes in electrode impedance or position or, as Paloheimo and Rantala [19] have suggested, it might be attributable to the disappearance of central enhancement of the evoked EMG response when the patient falls asleep.

In conclusion, we have demonstrated that gallamine and vecuronium are associated with significantly different degrees of TOF fade during onset (gallamine > vecuronium). However, during early spontaneous offset (T1 up to 50% of control) their fade profiles are similar and, during late spontaneous offset (T1 : control 75%), the situation is vecuronium > gallamine. Thus conclusions and assumptions previously made concerning the fade profiles of neuromuscular blocking drugs (and hence their pre- and postsynaptic effects), especially if based on work performed during the onset of neuromuscular blockade only, may not be valid.

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MAINTENANCE OF CONSTANT 95% NEUROMUSCULAR BLOCKADE BY ADJUSTABLE INFUSION RATES OF PANCURONIUM AND ATRACURIUM

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SUMMARY

In a double-blind study, 39 patients (ASA groups I–II,) were given either pancuronium or atracurium as an infusion during surgery. The drugs were given as an initial loading dose of 0.064 mg kg^{-1} or 0.30 mg kg^{-1}, respectively, followed by an infusion, the rate of which was regulated to produce a constant 95% depression of the evoked twitch response throughout surgery. No significant difference in the number of corrections of the infusion rate per hour was found (4.6 v. 4.9). Mean infusion maintenance doses were 35 and 356 µg kg^{-1} h^{-1}, respectively. The inter-individual variability of maintenance doses for the two drugs did not differ, the coefficients of variation being 0.32 and 0.24. On stopping the infusion, the patients given atracurium recovered to a 15% twitch faster than those given pancuronium. In addition neostigmine produced a quicker recovery in this group. Thus atracurium may be a more satisfactory drug for use by infusion.

Maintenance of neuromuscular blockade during surgery with the traditional non-depolarizing blockers (e.g. pancuronium) is achieved typically by an initial loading dose of the ED_{95} multiplied by 1.5–2, supplied with smaller increments as required on clinical judgement [1]. This strategy poses two problems: unstable and poorly controlled levels of neuromuscular blockade, and accumulation. The latter may involve residual relaxation or undue prolongation of anaesthesia until adequate antagonism of blockade has been achieved [2, 3]. The new non-depolarizing drugs of intermediate duration of action may be given by the same scheme, but more appropriately as an infusion.

The aim of this study was to assess how easily a fixed level of 95% blockade could be maintained by giving a bolus of pancuronium or atracurium followed by an infusion at a rate adjusted to maintain this level of blockade.

PATIENTS AND METHODS

Thirty-nine patients (ASA groups I–II) were studied during elective surgery requiring muscle relaxation for more than 45 min (table I). Except for one mastectomy, the operations performed were intra-abdominal gastrointestinal and gynaecological procedures. All patients gave informed consent to the study and approval had been obtained from the local Ethics Committee.

Exclusion criteria included: age below 20 yr or above 70 yr, neuromuscular disease and medication with tricyclic antidepressant, neuroleptic, aminoglycoside, peptide antibiotic or calcium antagonist drugs. An additional three patients

TABLE I. *Details of patients. Mean values (range)*

	Pancuronium	Atracurium
Patient number	19	20
Sex (M/F)	2/17	2/18
Age (yr)	49.4 (20–70)	45.6 (25–65)
Weight (kg)	66.0 (51–90)	65.4 (47.5–90)
Height (cm)	164 (152–179)	166 (158–177)

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were excluded during operation because of malfunction of the syringe driver or displacement of the armboard.

The patients were allocated randomly to receive either pancuronium or atracurium. The investigation was blinded so that both patient and anaesthetist were unaware of which drug was given.

Premedication comprised diazepam 0.3 mg kg^{-1} by mouth 1 h before surgery. Anaesthesia was induced with pethidine 1 mg kg^{-1} and thiopentone 3–5 mg kg^{-1} i.v. and maintained by means of 66 % nitrous oxide in oxygen and supplements of pethidine 0.3 mg kg^{-1} and thiopentone 0.8 mg kg^{-1}. All drugs were given through a constantly running infusion in a peripheral vein in the arm not suspended in the neuromuscular recording device.

Neuromuscular blockade was monitored by the use of a force displacement transducer measuring the evoked adduction force of the thumb. The transducer was interfaced to a Myograph 2000 (Biometer, Denmark). In each patient, resting thumb tension was maintained between 150 and 300 g during recordings. Supramaximal train-of-four (TOF) stimuli (2 Hz, 2 s) were delivered every 10 s to the ulnar nerve at the wrist via surface electrodes. Twitch height and TOF ratio were registered continuously digitally and on a chart recorder.

When stable neuromuscular recordings had been obtained, typically 5–10 min after induction, a bolus was given of pancuronium 0.064 mg kg^{-1} or atracurium 0.3 mg kg^{-1} (equipotent doses). The trachea was intubated when the evoked response of the adductor pollicis had declined to zero.

Maintenance of stable neuromuscular blockade was achieved by the i.v. infusion of pancuronium 0.1 mg ml^{-1} or atracurium 1 mg ml^{-1} (Dameca Injectomat syringe driver). The infusion (initial infusion rates of 0.037 mg kg^{-1} h^{-1} or 0.37 mg kg^{-1} h^{-1}, respectively) was commenced when the first response to TOF stimulation had recovered to 5 %. Bolus doses and initial infusion rates were found in earlier studies to be equipotent [4, 5]. Infusion rates were adjusted in order to preserve the twitch height between 1 and 10 % of the initial values throughout surgery. The magnitude of the adjustments was approximately 25 % of the initial infusion rate and at least 5 min elapsed between adjustments.

Infusions were discontinued 10–15 min before the termination of surgery and residual block was antagonized by neostigmine 2.5 mg and atropine 1 mg i.v. when twitch height had reached 15 %. The block was considered fully antagonized when the TOF ratio was 0.7.

Arterial blood-gas analysis was performed during surgery and confirmed that normocapnia had been achieved. Heart rate and ECG were monitored continuously and non-invasive arterial pressure was recorded automatically at 5-min intervals (Dinamap, Criticon).

Skin temperature on the stimulated hand and temperature in the nasopharynx were measured at the beginning and end of anaesthesia.

The Wilcoxon Rank Sum Test was used for statistical analyses. $P < 0.05$ was chosen as the level of significance.

RESULTS

The two groups were comparable with respect to age, weight, height and sex ratio (table I). Characteristics of the block in each group as shown in table II.

Average maintenance doses of pancuronium and atracurium were found to be 35 μg kg^{-1} h^{-1} (range 17.6–58.3, SD 11.1) and 356 μg kg^{-1} h^{-1} (range 207–531, SD 87.2), respectively. Comparisons of dispersion in the two groups were made by calculation of F:

$$F = \frac{(\text{SD pancuronium divided by mean})^2}{(\text{SD atracurium divided by mean})^2}$$

yielding no significant difference.

TABLE II. *Characteristics of neuromuscular blockade. Mean values (range). Statistical significance by Wilcoxon's rank sum test*: *P < *0.05*

	Pancuronium	Atracurium
Time from bolus to maximal blockade (s)	138 (80–240)	116.5* (70–420)
Duration of action from administration of bolus to 5 % recovery (min)	26.6 (6–45)	26.0 (0–39)
Duration of infusion (min)	65 (23–165)	71 (22–177)
Spontaneous recovery from 5 % to 15 % (min)	25 (10.5–37)	15* (6–34)
Reversal by neostigmine from 15 % to TOF ratio 0.7 (min)	10.0 (4.5–17)	6.5* (3–11)

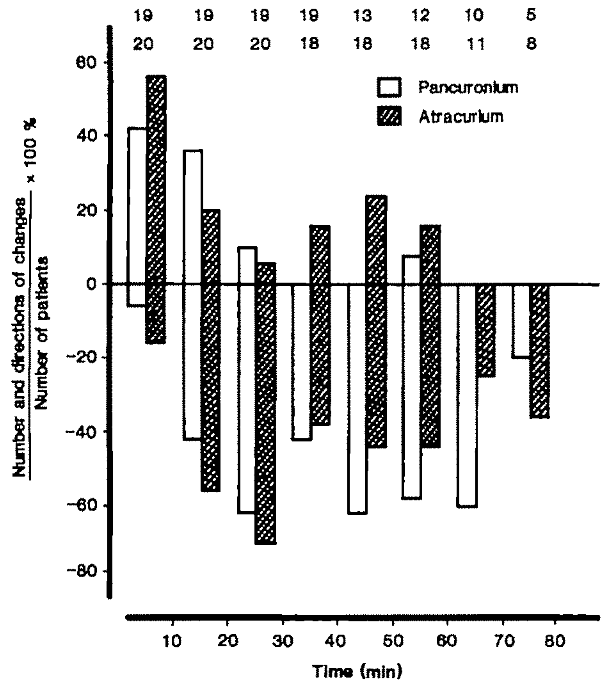

FIG. 1. Number and direction of changes of the infusion rate of pancuronium and atracurium expressed as percentages of number of patients during successive 10-min intervals. Initial infusion rates were 37 µg kg^{-1} h^{-1} and 370 µg kg^{-1} h^{-1}, respectively, and the size of corrections approximately 25 % of the initial rate. Numbers above bars refer to number of patients.

On average 4.6 (range 1–8) corrections per hour were required in the pancuronium group compared with 4.9 (range 2–10) in the atracurium group. Figure 1 shows the frequency and mode of adjustment of the infusion rate in successive 10-min intervals. The typical pattern of infusion rates in both groups was an increase during the first 10 min of infusion. In both groups the initial infusion rate (which was close to the average maintenance dose) had to be increased in approximately 50 % of patients in order to maintain 95 % blockade. Thereafter a slow but steady decline was seen in the pancuronium group, whereas six of 20 patients receiving atracurium had to be given increasing amounts of the drug after a further 20 min. The rate of adjustment of the infusion rate diminished only slightly with time and this is shown in figure 1 by a decreasing bar length.

The mean temperature of the nasopharynx at induction was 36.0 °C in both groups. At the end of anaesthesia it had decreased 0.5 °C in the pancuronium group and 0.6 °C in the atracurium group. Mean skin temperature of the stimulated hand was 32.4 °C and 32.2 °C and this decreased by 0.3 °C and 0.4 °C, respectively. In 10 patients, dispersed evenly in both groups, skin temperature increased by 0.1–2.0 °C.

DISCUSSION

We have confirmed that the time of onset from administration of the bolus to maximal blockade, the rate of spontaneous recovery from 5 % to 15 % and the duration from this point to full recovery produced by neostigmine were shorter for atracurium than pancuronium.

The durations of action from administration of the bolus to 5 % recovery of the first twitch response were surprisingly similar, 26.6 min and 26.0 min for the pancuronium and atracurium groups, respectively. After a bolus dose of pancuronium 0.075 mg kg^{-1} and atracurium 0.33 mg kg^{-1} Gramstad, Lilleaasen and Minsaas [4] found a duration of action to 25 % recovery of 45.1 min and 27.6 min. Our results are explained partly by the fact that spontaneous reversal is shorter for atracurium than for pancuronium. Hence, the time required to recover from 5 % to 25 % is considerably longer for pancuronium than atracurium. The relatively small bolus doses used in this study (ED_{95}) were not sufficient to suppress twitch response completely in all patients (six in the pancuronium group and three in the atracurium group). This may also account for measured duration of action, because kinetics may be influenced predominantly by redistribution rather than elimination of the drugs under these conditions.

The maintenance doses of pancuronium and atracurium used during infusion (35 and 356 µg kg^{-1} h^{-1}) are comparable to those found elsewhere [5–8]. The inter-individual variations of atracurium pharmacodynamics are claimed to be relatively small compared with other non-depolarizing drugs as a result of the unique and rather uniform rate of Hoffman elimination [9]. This was not confirmed in our study. Although we found a slightly smaller standard deviation and range (in relation to mean) for the average maintenance dose of atracurium as opposed to pancuronium, the difference was not significant.

The two drugs did not differ in respect of ease of control—four to five regulations of the infusion rate were required per hour to maintain 95 %

blockade. However, the pattern of infusion rates differed, as shown in figure 1. We believe that this reflects different cumulative properties of the drugs, being smaller for atracurium.

Simpler infusion regimens inevitably lead to unacceptable variations of the level of relaxation when using a pre-fixed rate of infusion, because of inter-individual variation in dose responses. With a non-cumulative drug, many patients probably maintain a constant level of block, but not necessarily the level desired. Of course, one may choose an infusion rate large enough to keep the majority of the patients sufficiently relaxed, but this involves a considerable variation in the duration from the end of infusion to the point at which administration of an antagonist is effective. The quick spontaneous rate of antagonism of atracurium may partly obviate this problem. However, careful monitoring of the block is still necessary to ensure safe antagonism [2].

The temperature changes in the hand were small and of similar magnitude in both groups and are unlikely to have influenced our results. The difference in peripheral to central temperature gradient was not significant between groups. It is notable that the peripheral temperature increased in 10 patients, and it is likely that vasodilatation produced by pethidine was responsible.

In conclusion we have shown that, in order to maintain a uniform level of surgical relaxation produced by a bolus dose followed by infusion of pancuronium or atracurium, frequent and large corrections of the rate of infusion are necessary. With atracurium, at least as many adjustments of the rate of infusion are required as with pancuronium. However, the use of atracurium is associated with quicker spontaneous and induced reversal.

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DIFFERENTIAL EFFECTS OF CALCIUM CHANNEL BLOCKING AGENTS ON PANCURONIUM- AND SUXAMETHONIUM-INDUCED NEUROMUSCULAR BLOCKADE

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Calcium channel blocking agents are a chemically heterogeneous group of drugs that inhibit the ionic current carried through the calcium slow channel in cardiac and vascular smooth muscle. This action is the basis of their usefulness in the treatment of cardiovascular disorders [1].

Although the role of calcium in skeletal muscle differs from that in cardiac and vascular smooth muscle, various recent studies have shown that verapamil is able to inhibit neuromuscular function *in vitro* and *in vivo* in skeletal muscle preparations from experimental animals [2–7]. Moreover, verapamil has been reported to induce respiratory failure in a patient with Duchenne's dystrophy [8].

Verapamil and nifedipine have been shown also to increase the muscular paralysis induced by several non-depolarizing neuromuscular blocking drugs in isolated preparations [9–11] and in intact animals [12–14]. In addition, the neuromuscular blockade induced by vecuronium was prolonged in a patient treated with verapamil [15]. However, it is not well known if calcium channel blocking agents modify the effects of depolarizing neuromuscular blocking drugs.

The present study was undertaken to determine if nicardipine, verapamil and diltiazem could potentiate the effects of suxamethonium, and to compare their effects on suxamethonium- and pancuronium-induced neuromuscular blockade.

SUMMARY

The effects were studied of several calcium channel blocking agents on muscle twitch, and possible interactions between these drugs and pancuronium and suxamethonium, using a rat phrenic–hemidiaphragm preparation. Nicardipine, verapamil and diltiazem each caused a concentration-related depression of muscle response. Nicardipine had the most, and diltiazem the least, potent effect. Verapamil and diltiazem 5 and 10 µmol litre^{-1} caused a concentration-dependent enhancement of suxamethonium-induced neuromuscular blockade, but increased the effect of pancuronium only at 10 µmol litre^{-1}. Nicardipine 10 µmol litre^{-1} significantly enhanced pancuronium-induced neuromuscular blockade, but not that produced by suxamethonium.

MATERIAL AND METHODS

Animals and procedure

Phrenic–hemidiaphragm preparations from female Wistar rats (200–250 g), obtained as described by Bulbring [16], were immersed in Krebs solution (NaCl 5.5 g, KCl 0.35 g, $MgSO_4.7H_2O$ 0.29 g, $CaCl_2.2H_2O$ 0.28 g, $KHPO_4$ 0.16 g, $NaHCO_3$ 2.1 g and glucose 2.1 g in 1 litre of deionized water) maintained at 37 ± 1 °C and bubbled with oxygen containing 5% carbon dioxide.

Contractions were induced by phrenic nerve stimulation at a frequency of 0.1 Hz with supramaximal 0.2-ms rectangular pulses, as described

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by Foldes [17], and recorded isometrically with a Letica transducer interfaced to a Beckman polygraph.

Before the experiments were carried out each preparation was subjected to a tension of 1 g and the phrenic nerve was stimulated every 15 min for 1 h to obtain stable basal conditions. After this, cumulative concentration–response curves were obtained with each drug or association of drugs. The effect of each concentration of the drug studied was evaluated 10 min after addition to the bath. Only one concentration–response curve was obtained with each preparation.

Drugs

In the first part of the study, when the effects of each drug alone were evaluated, the concentrations used were: nicardipine 5–100 μmol $litre^{-1}$, verapamil 10–50 μmol $litre^{-1}$, diltiazem 10–250 μmol $litre^{-1}$, pancuronium 1–5 μmol $litre^{-1}$ and suxamethonium 6–34 μmol $litre^{-1}$. In the second part of the study, when the interaction between calcium channel and neuromuscular blocking agents was evaluated, nicardipine, verapamil and diltiazem were used at constant concentrations (5 and 10 μmol $litre^{-1}$), whereas pancuronium and suxamethonium were used at the concentrations described above. Fresh solutions of all drugs were prepared in deionized water immediately before use. Solutions of nicardipine were protected carefully from light before and during the experiments since this drug is unstable in natural light.

Analysis of results

Changes in twitch height were expressed as percentage of control twitch height. The concentrations of drugs required to produce 50% inhibition of muscular contractions (IC_{50}) were determined from computer derived log dose–response regression lines. Differences between values were analysed by Student's *t* test for non-paired data, $P < 0.05$ being regarded as significant.

RESULTS

Effects of calcium channel and neuromuscular blocking drugs on indirectly-elicited diaphragm contractions

Nicardipine, verapamil and diltiazem produced concentration-dependent inhibition of diaphragm contraction (fig. 1). The IC_{50} figures (mean ± SD) were 22.8 ± 15.1 μmol $litre^{-1}$ for nicardipine, 27.3 ± 5.3 μmol $litre^{-1}$ for verapamil and 73.1 ± 9.3 μmol $litre^{-1}$ for diltiazem. The greatest concentration used of each agent totally abolished indirectly-elicited muscle contraction.

As expected, pancuronium and suxamethonium also induced a concentration-dependent neuromuscular blockade (figs 2, 3). Their IC_{50} were 2.9 ± 0.2 μmol $litre^{-1}$ and 18.7 ± 2.8 μmol $litre^{-1}$, respectively.

Interactions between calcium channel blocking agents and suxamethonium

Nicardipine 5 and 10 μmol $litre^{-1}$ did not significantly enhance suxamethonium-induced neuromuscular blockade (fig. 2A), nor did it modify the IC_{50} of suxamethonium (table I).

Verapamil 5 and 10 μmol $litre^{-1}$ significantly enhanced the neuromuscular blocking activity of suxamethonium, producing a shift to the left of the suxamethonium concentration–response curve (fig. 2B). The displacement obtained with 10 μmol $litre^{-1}$ was greater than that produced by 5 μmol $litre^{-1}$ (fig. 2B) and the IC_{50} of suxamethonium decreased proportionately (table I). A similar response was obtained with diltiazem, which at 5 and 10 μmol $litre^{-1}$ increased significantly the neuromuscular blockade produced by

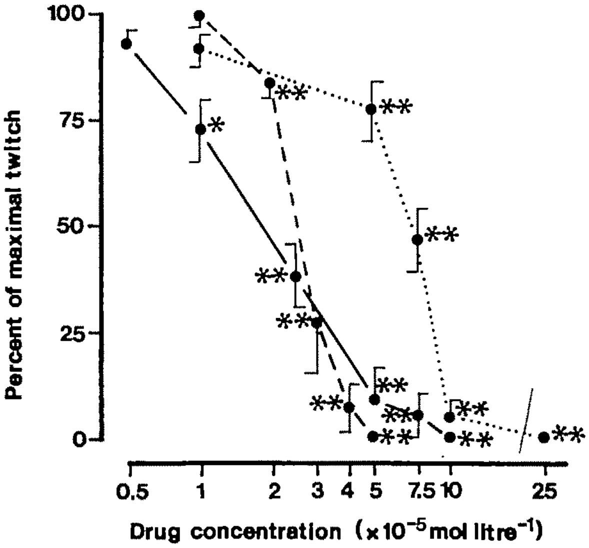

FIG. 1. Effects of nicardipine (——), verapamil (——) and diltiazem (·······) on indirectly elicited diaphragm contractions. Each point represents the mean ± SEM of six to 10 experiments. $*P < 0.05$; $**P < 0.01$ compared with control values (Student's *t* test).

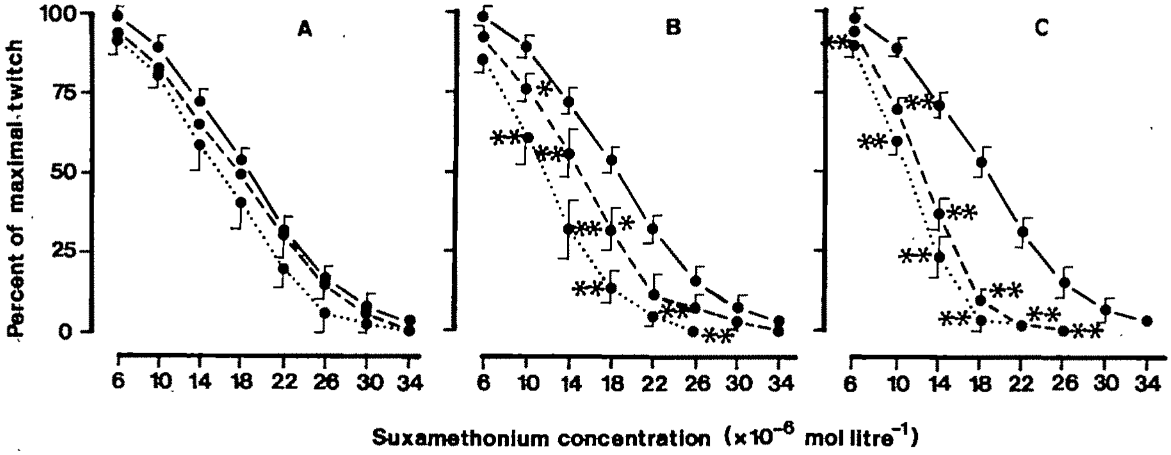

FIG. 2. Effects of calcium channel blockers and suxamethonium on indirectly elicited diaphragm contractions. A: Effects of suxamethonium (——), suxamethonium + nicardipine 5 μmol litre^{-1} (– – –) and suxamethonium + nicardipine 10 μmol litre^{-1} (.....). B: Effects of suxamethonium (——), suxamethonium + verapamil 5 μmol litre^{-1} (– – –) and suxamethonium + verapamil 10 μmol litre^{-1} (.......). C: Effects of suxamethonium (——), suxamethonium + diltiazem 5 μmol litre^{-1} (– – –) and suxamethonium + diltiazem 10 μmol litre^{-1} (......). Each point represents the mean ± SEM of six to 10 experiments. $^{*}P < 0.05$; $^{**}P < 0.01$ compared with suxamethonium alone (Student's t test).

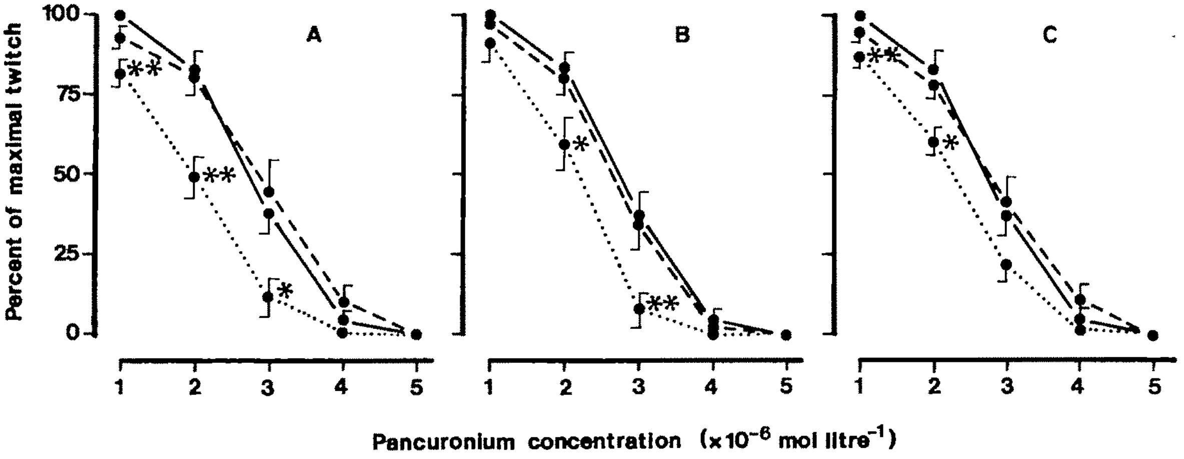

FIG. 3. Effects of calcium channel blockers and pancuronium on indirectly elicited diaphragm contractions. A: Effects of pancuronium (——), pancuronium + nicardipine 5 μmol litre^{-1} (– – –) and pancuronium + nicardipine 10 μmol litre^{-1} (......). B: Effects of pancuronium (——), pancuronium + verapamil 5 μmol litre^{-1} (– – –) and pancuronium + verapamil 10 μmol litre^{-1} (.....). C: Effects of pancuronium (——), pancuronium + diltiazem 5 μmol litre^{-1} (– – –) and pancuronium + diltiazem 10 μmol litre^{-1} (......). Each point represents the mean ± SEM of six to 10 experiments. $^{*}P < 0.05$; $^{**}P < 0.01$ compared with pancuronium alone (Student's t test).

suxamethonium (fig. 2C) and elicited a concentration-dependent decrease in the IC_{50} of suxamethonium (table I).

Interaction between calcium channel blocking agents and pancuronium

Nicardipine 10 μmol litre^{-1}, but not 5 μmol litre^{-1} significantly enhanced pancuronium-induced neuromuscular blockade (fig. 3A), decreasing its IC_{50} (table I). A similar pattern of response was obtained with verapamil and diltiazem which produced a significant enhancement of pancuronium effects only at a concentration of 10 μmol litre^{-1}, causing a displacement of its concentration–response curve to the left (fig. 3B and 3C) and a decrease in the IC_{50} (table I).

TABLE I. *Inhibitory concentration 50* (IC_{50}) *(μmol litre*$^{-1}$*) of suxamethonium and pancuronium alone and in combination with different concentrations of calcium channel blockers. Mean ± SD of the number of experiments* (n) *shown in parentheses.* $^{*}P < 0.05$; $^{**}P < 0.01$ *compared with control values (Student's* t *test)*

Pretreatment	Suxamethonium	(*n*)	Pancuronium	(*n*)
—	18.7±2.8	(10)	2.9±0.2	(10)
Nicardipine 5 μmol litre^{-1}	17.9±4.0	(8)	3.1±0.5	(6)
Nicardipine 10 μmol litre^{-1}	16.1±3.1	(8)	2.0±0.4**	(8)
Verapamil 5 μmol litre^{-1}	14.4±2.7*	(8)	2.7±0.4	(6)
Verapamil 10 μmol litre^{-1}	11.7±3.4**	(6)	2.1±0.3**	(8)
Diltiazem 5 μmol litre^{-1}	12.4±1.2**	(6)	2.8±0.4	(6)
Diltiazem 10 μmol litre^{-1}	11.1±1.3**	(6)	2.3±0.3**	(8)

DISCUSSION

Our results show that several calcium channel blocking agents produce a significant decrease in rat diaphragm muscle twitch and potentiate the effects of suxamethonium and pancuronium to differing degrees.

Verapamil, diltiazem and nicardipine caused a concentration-dependent inhibition of muscle contraction. These effects are similar to those reported previously with verapamil using the same preparation [2, 5, 7]. The concentrations of calcium channel blocking agents necessary to depress muscle twitch response (10–250 μmol litre^{-1}) are greater than those needed to induce cardiac or vascular smooth muscle effects [18], suggesting that skeletal muscle effects might be related to factors other than calcium channel blockade. In this sense it is interesting to note that verapamil and diltiazem produced a local anaesthetic effect at concentrations greater than 10 μmol litre^{-1} [19, 20]. However, nicardipine is devoid of such effect [21], and it is conceivable that its activity on skeletal muscle may be a consequence of its action on the calcium channel.

On the other hand, we have found that verapamil increased the effects of pancuronium and suxamethonium, as has been reported by others [2, 9, 12, 13]. We have also shown that diltiazem, but not nicardipine, increased the effect of suxamethonium, whereas both drugs enhanced pancuronium-induced blockade. These interactions cannot be related to the local anaesthetic activity mentioned above, because nicardipine lacks such activity and verapamil and diltiazem exert it only at greater concentrations than were used in this part of the study (5 and 10 μmol litre^{-1}). Instead, the increase in the effects of pancuronium may be related to the calcium channel blockade induced by these drugs. Two facts suggest this hypothesis: pancuronium-induced neuromuscular blockade is antagonized by calcium [17, 22] and by 4-aminopyridine, which increases transmembrane calcium influx [17]; and, at equimolecular concentrations, nicardipine increased the effects of pancuronium to a greater degree than verapamil, which in turn produced a greater increase than diltiazem. This order of potency is the same as that shown by these drugs as inhibitors of calcium-induced contractions in vascular smooth muscle [18, 23, 24].

The blockade induced by suxamethonium in rat phrenic–hemidiaphragm preparations is antagonized also by calcium and 4-aminopyridine [17] and, consequently, the increase in suxamethonium effect caused by calcium channel blocking agents in the present study was not unexpected. The observed potency in increasing suxamethonium-induced neuromuscular blockade was: diltiazem > verapamil > > nicardipine,—that is the opposite of their potency in enhancing pancuronium-induced neuromuscular blockade. The reasons for this difference are difficult to clarify. Apparently, the differing capacity of calcium channel blocking agents to increase the effects of pancuronium and suxamethonium may be related to the different mechanisms of action of non-depolarizing and depolarizing neuromuscular blocking drugs. Suxamethonium depolarizes skeletal muscle fibres [25], and the calcium channel blocking activity of diltiazem and verapamil, but not that of dihydropyridines, increases proportionately with the degree of membrane depolarization [26, 27]. However, this may be too simple an explanation as the rat diaphragm *in vitro* shows some spontaneous recovery of resting potential following depolarization by suxamethonium or other depolarizing drugs [28, 29]. Thus the nature of this interaction is more complex than that suggested.

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INFLUENCE OF EXTRADURAL AND GENERAL ANAESTHESIA ON NATURAL KILLER CELL ACTIVITY AND LYMPHOCYTE SUBPOPULATIONS IN PATIENTS UNDERGOING HYSTERECTOMY

E. TØNNESEN AND C. WAHLGREEN

Summary

The effect of hysterectomy was studied on natural killer (NK) cell activity, the distribution of lymphocyte subpopulations, and the endocrine stress response in 16 patients allocated to receive extradural analgesia S5–T4 (group I) or neuroleptanaesthesia (NLA) (group II). In group II a significant decrease in NK cell activity was found after operation for at least 3 days, while surgery during extradural analgesia did not induce significant changes. The impaired NK cell activity was accompanied by leucocytosis and lymphopenia affecting the T-lymphocytes (OKT3$^+$ and OKT4$^+$), the B-lymphocytes (B1$^+$) and NK cells (Leu 11$^+$). Compared with group II, extradural analgesia significantly reduced the cortisol and noradrenaline response to surgery, while the adrenaline response in both groups was abolished. The results suggest that the decrease in NK cell activity and alterations in lymphocyte subsets induced by surgery and general anaesthesia can be prevented to a certain degree by extradural analgesia.

There is substantial evidence indicating that anaesthesia and surgery produce significant suppression of immune defences [1–3] and it has been suggested that this may increase the risk of postoperative infection [3, 4] and contribute to the dissemination of solid tumours [5].

Natural killer (NK) cells are a subpopulation of large granular lymphocytes showing spontaneous cytotoxicity against certain tumour cells, virus infected cells and some primitive normal cells [6, 7]. Although the exact role of NK cells *in vivo* remains debatable, there is increasing evidence that the NK cell system plays an important role as a primitive first line defence against certain malignancies and microbial infections [8, 9].

Previous investigations have shown an increased NK cell activity during premedication, anaesthesia and surgery [10–13] followed by a pronounced reduction in postoperative activity of 3–6 days duration after major surgery [12–18] and only slight changes after minor surgery [19].

The mechanisms accounting for the intra- and postoperative fluctuations in NK cell activity are unknown, but it has been suggested that the endocrine stress response is important [17, 19].

Measurements of serum cortisol and plasma adrenaline concentrations are prominent markers of this response. Several studies have demonstrated that cortisol and adrenaline exert opposite effects on the NK cell system with adrenaline enhancing [20–23] and cortisol inhibiting the activity *in vitro* and *in vivo* [24].

Extradural blockade extending from T4 to S5 either reduces or prevents the endocrine metabolic response associated with lower abdominal surgery (for review, see Kehlet [25]). So far only one study has examined NK cell activity after lower abdominal surgery performed during extradural analgesia [17]. However, the endocrine response to surgery was not measured on that occasion.

The present study was designed to examine the effects of extradural and general anaesthesia on NK cell activity, the distribution of lymphocyte subsets, and the endocrine stress response in patients undergoing hysterectomy.

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TABLE I. *Comparative demographic and clinical data of patient groups. Median values (range). No significant differences between groups*

	Group I Extradural	Group II NLA
n	8	8
Age (yr)	41 (36–48)	45 (40–50)
Weight (kg)	60 (48–68)	64 (55–78)
Duration of general anaesthesia before surgery (min)		35 (25–60)
Duration of operation (min)	85 (75–110)	75 (60–85)

PATIENTS AND METHODS

Sixteen pre-menopausal women undergoing abdominal hysterectomy because of non-malignant metrorrhagia were studied. Informed consent was obtained from all patients and the study was approved by the Regional Ethics Committee on Human Research. No patient was suffering from cancer, renal, hepatic, endocrine or cardiopulmonary disease and none received any medical treatment. The patients were allocated randomly to two groups of eight each (table I).

Anaesthetic techniques

Premedication consisted of morphine sulphate 10 mg and hyoscine 0.4 mg i.m., 60–90 min before the scheduled time of operation. The operations started between 8 and 10 a.m. and all anaesthetics were administered by the same anaesthetist.

Group I extradural analgesia. Before the procedure each patient received 400–500 ml of isotonic saline. An extradural catheter was inserted at the L4–5 space and analgesia induced with 0.5% bupivacaine plain. The technique has been described in detail previously [13]. Analgesia, extending from T4 to S5, was confirmed by pinprick before skin incision and additional doses of 0.5% bupivacaine plain were given during operation. After operation, analgesia was maintained until next morning using 0.25% bupivacaine plain 7–9 ml h^{-1} administered into the extradural space by infusion pump. In addition, supplementary doses of 0.25% bupivacaine 10 ml were given when needed.

Group II neuroleptanaesthesia (NLA). Anaesthesia was induced with droperidol 0.25 mg kg^{-1} and fentanyl 0.005 mg kg^{-1}, and tracheal intubation was performed after administering pancuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with 66% nitrous oxide in oxygen. Pulmonary ventilation was controlled to normocapnia by an MCM 801 ventilator (Dameca, Denmark). Supplementary doses of fentanyl, droperidol and pancuronium were given as judged by the clinical needs of the patients. At the end of surgery residual neuromuscular blockade was antagonized with a mixture of atropine and neostigmine.

In both groups, i.v. infusions during surgery were restricted to isotonic saline in glucose. During the first 1 h it was infused at a rate of 10–15 ml kg^{-1} and thereafter at 1–2 ml kg^{-1} h^{-1}. Blood loss of up to 500 ml was replaced with isotonic saline 2.5 ml in glucose per ml of blood loss. Haemorrhage did not exceed 500 ml and blood substitutes or sympathomimetic agents were not required.

Postoperative care

All patients were observed in the intensive care unit until the day after surgery. For postoperative analgesia, patients in group I were given extradural morphine in a dose of 5 mg three times a day starting on the first day after operation and continued for 2–4 days. In group II nicomorphine (Vilan) was administered parenterally (i.v. or i.m.) on demand.

Blood sampling

Sampling of venous blood was performed as shown in figure 1, for determination of NK cell activity, distribution of lymphocyte subpopulations, blood leucocyte counts, and measurement of serum cortisol, plasma adrenaline and noradrenaline concentrations. Sample IVa was taken for cortisol measurements only. All pre- and postoperative samples were taken between 9 and 11 a.m.

Assay for NK cell cytotoxicity

Separation of mononuclear cells, cryopreservation and determination of NK cell cytotoxicity were performed as described in detail previously [12].

Briefly, mononuclear cells were isolated by Ficoll-Hypaque (Lymfoprep, Nyegaard & Co., Oslo, Norway) gradient centrifugation. The cells were cryopreserved and stored in liquid nitrogen (−180 °C) until all specimens from each patient could be tested at the same time against K562 target cells in a 6-h ^{51}Cr-release assay.

All assays were performed in duplicate at effector : target cell ratios of 50 : 1, 25 : 1 and 12.5 : 1,

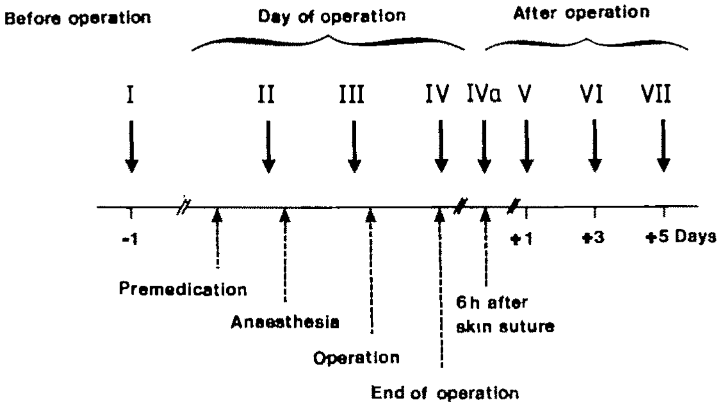

FIG. 1. Eight venous blood samples taken from each patient before, during and after operation are indicated by arrows. Blood was drawn the day before operation (sample I). On the day of operation, sample II was taken after administration of premedication immediately before induction of anaesthesia, sample III during anaesthesia before skin incision, sample IV at the completion of surgery, and sample IVa 6 h after skin suture. After operation three blood samples (V, VI and VII) were drawn.

with the results representing the first mentioned ratio.

NK cell activity was expressed as percentage of cytotoxicity according to the formula:

$$\% \text{ cytotoxicity} = \frac{\text{cpm exptl release} - \text{cpm spont. release}}{\text{cpm max. release} - \text{cpm spont. release}} \times 100$$

where cpm = counts per minute, exptl = experimental, max. = maximum, spont. = spontaneous.

Spontaneous release was the radioactivity released from target cells in the growth medium, and maximum release was the radioactivity released when the target cells were frozen and thawed three times in distilled water. Spontaneous release never exceeded 20% of maximum release. The analytical within variation of the NK cell cytotoxicity assay was estimated by 20 simultaneous measurements of one specimen of mononuclear cells. The coefficient of variation (CV) was 5%. The interindividual and intraindividual variations were calculated from two consecutive "day-to-day" samples from 24 healthy volunteers. The interindividual CV was 58% while the intraindividual CV was 13%.

Analysis of lymphocyte subpopulations by indirect immunofluorescence

For determinations of lymphocyte subpopulations, the lymphocytes were thawed, washed and adjusted to 0.5×10^6 cells per test tube in 0.5 ml of TC-199 medium (Gibco, Bio-Cult, Glasgow). After centrifugation at 500 *g* for 10 min, the supernatant was removed from the tubes. The technique has been described in detail previously [23].

The monoclonal antibody Leu II (Becton Dickinson, Becton Dickinson Monoclonal Center, Inc., California, U.S.A.) was used to characterize NK cells. The pan T-cell population was quantitated with OKT3 antibody (Ortho-Mune Series, Ortho Diagnostic Systems Inc., New Jersey, U.S.A.), the T-helper cells with OKT4 antibody, and the T-suppressor/cytotoxic cells with OKT8 antibody. The B-cell population was estimated with the monoclonal antibody B1 (Coulter Clone, Coulter Immunology, Florida, U.S.A.).

The cells (20000–100000) were analysed by indirect immunofluorescence in an Epics C (Coulter Electronics Inc., Hialeah, Florida, U.S.A.) fluorescence activated cell sorter and the fluorescence intensity measured on a single cell basis at 525 nm after excitation at 488 nm with an Argon laser (500 mW). The percentage of cells positive for the various specific antibodies was calculated after subtracting the number of cells reacting with ascites from non-secreting hybridoma.

Leucocyte and differential count

The total leucocyte counts were performed using a Coulter Counter S (Coulter Electronics, England) and the differential counts were performed automatically (Model 360, Hematrach, Geometric Data, England).

Endocrine evaluation

Plasma adrenaline and noradrenaline concentrations were measured by high pressure cation exchange chromatography with electrochemical detection [26]. Serum cortisol concentrations were measured by a competitive protein binding technique [27].

Statistical analysis

The results obtained in each of the two groups were first analysed by a one-way analysis of variance (Friedman's test for related samples). If the test resulted in rejection of the null hypothesis, multiple comparisons of intragroup differences were performed according to Conover [28]. Finally, differences between the groups were analysed by the Mann-Whitney test. Values of $P < 0.05$ were considered to indicate statistical significance.

RESULTS

There was no difference in age, weight, or duration of surgery between the two groups (table I).

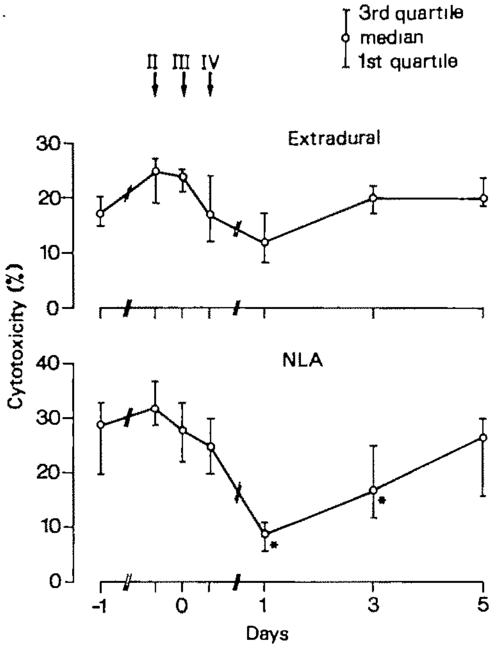

FIG. 2. NK cell activity expressed as percent cytotoxicity before, during and after hysterectomy in patients anaesthetized with extradural analgesia (group I) or neuroleptanaesthesia (NLA, group II). Median values and 1st and 3rd quartiles are shown. *Significant difference between preoperative value and the indicated value ($P < 0.05$).

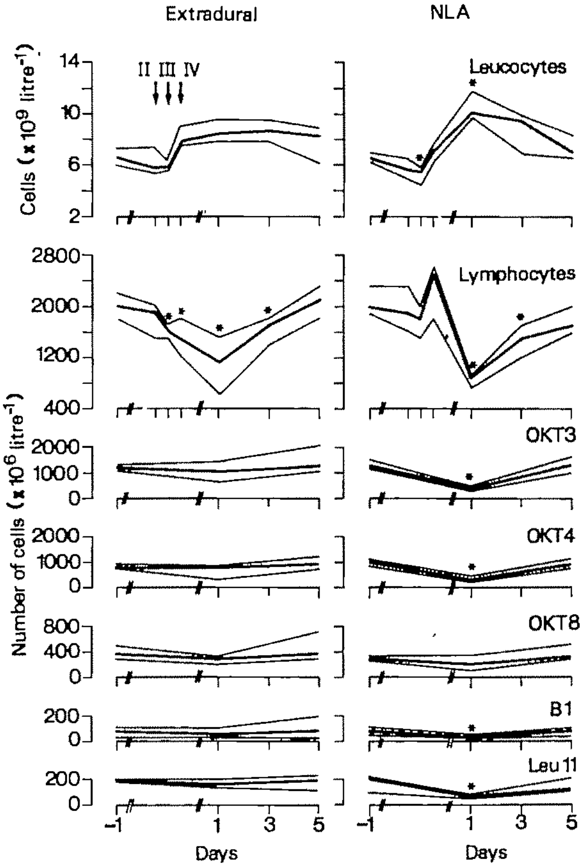

FIG. 3. Absolute number of circulating leucocytes, lymphocytes and lymphocyte subpopulations before and after hysterectomy. OKT3 antibody identified total T-cells, OKT4 the T-helper cells, OKT8 the T-suppressor cells, B1 the B-cells, and Leu 11 the NK cells. Median values and 1st and 3rd quartiles are shown. *Significant difference between preoperative value and the indicated value ($P < 0.05$).

In group I 145 mg (130–220 mg) (median, range) 0.5% bupivacaine was given during operation, and in group II fentanyl 0.70 mg (0.45–1.0 mg), droperidol 17.5 mg (12.5–25.0 mg) and pancuronium 8 mg (7–8 mg) were given.

NK cell cytotoxicity

Compared with preoperative values, the NK cell activity increased slightly, although not significantly, during premedication (sample II). After operation, the activity was reduced significantly for at least 3 days in group II, while no changes were found in group I (fig. 2). Comparing the two groups together there was no significant difference at any stage.

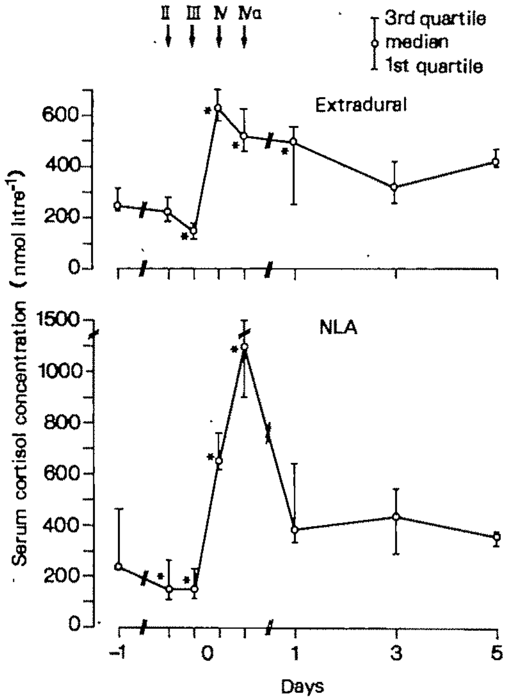

FIG 4. Serum cortisol concentration before, during and after hysterectomy in patients anaesthetized with extradural analgesia (group I) or NLA (group II). Median values and 1st and 3rd quartiles are shown. *Significant difference between preoperative value and the indicated value ($P < 0.05$).

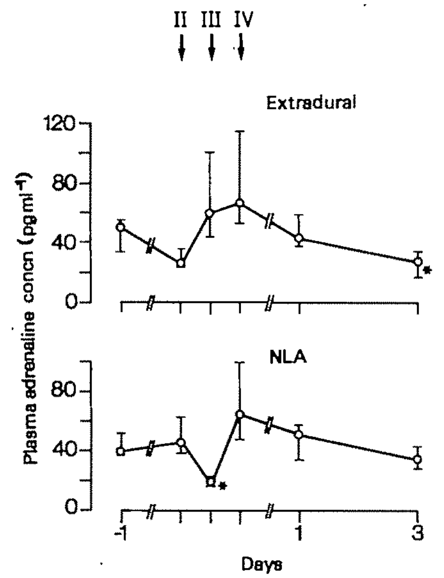

FIG. 5. Plasma adrenaline concentration before, during and after hysterectomy in patients anaesthetized with extradural analgesia (group I) or NLA (group II). Median values and 1st and 3rd quartiles are shown. *Significant difference between preoperative value and the indicated value ($P < 0.05$).

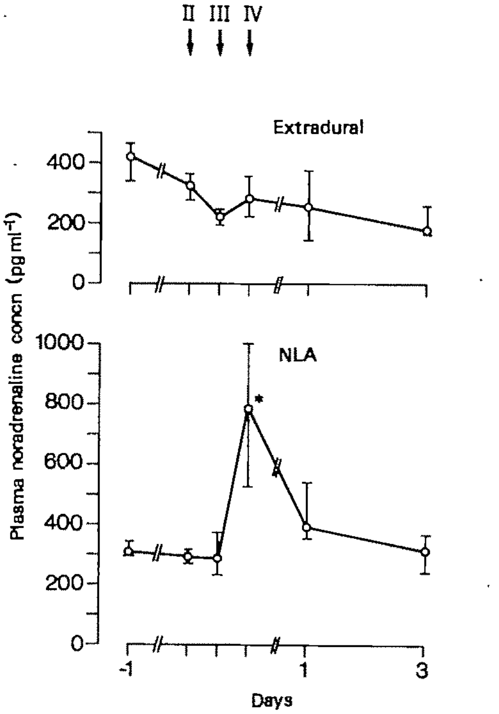

FIG. 6. Plasma noradrenaline concentration before, during and after hysterectomy. Median values and 1st and 3rd quartiles are shown. *Significant difference between preoperative value and the indicated value ($P < 0.05$).

Leucocyte counts and lymphocyte subpopulations

Significant leucocytosis and lymphopenia occurred after operation in group II, while only significant lymphopenia was found in group I (fig. 3).

The distribution of lymphocyte subpopulations was determined the day before surgery (−1) and on the 1st and 5th days after operation. The calculated number of lymphocytes reacting with monoclonal antibodies characterizing the subsets are shown in figure 3. The postoperative lymphopenia in group II was associated with a significant decrease in the number of all subsets with the exception of the T-suppressor (OKT8$^+$) cells, while no significant changes occurred in group I. There were no significant differences between the groups.

The hormonal responses

Premedication, general anaesthesia and extradural analgesia were accompanied by a gradual decrease in serum cortisol concentrations followed by an increase to peak concentrations at the completion of surgery (group I) or 6 h after skin suture (group II) (fig. 4). Compared with the NLA group, the cortisol response was reduced significantly by extradural analgesia.

Plasma adrenaline concentrations did not change significantly in group I in relation to premedication, analgesia and surgery, while a significant decrease was demonstrated after operation on day 3 (fig. 5). In group II the only significant change in plasma adrenaline concentration consisted of a decrease during anaesthesia (sample III).

Plasma noradrenaline concentration increased markedly at the completion of surgery in the NLA group, and this peak concentration greatly exceeded the noradrenaline values measured in the extradural group (fig. 6).

DISCUSSION

Both humoral and cellular factors may influence NK cell activity during and after anaesthesia and surgery [14, 17, 29]. The main purpose of the present study was to evaluate the interaction between NK cell activity, endocrine stress response, and distribution of circulating lymphocyte subpopulations, representing both humoral and cellular aspects.

The postoperative decrease in NK cell activity demonstrated in the NLA group is consistent with the findings after major surgery in previous studies [12, 13, 16, 17]. In addition, our observation that the reduction in NK cell activity could be prevented to a certain degree by extradural analgesia confirms the study by Ryhänen and colleagues [17], who demonstrated that extradural analgesia prevented the postoperative decrease in NK cell activity found after Caesarean section during general anaesthesia. However, in both the present study and that of Ryhänen the differences in NK cell activity between the studied groups were not significant.

The mechanisms underlying inhibition of NK cell activity after surgery are unknown, but our results suggest that the mediators of this immune suppression are affected by extradural analgesia.

Increased serum cortisol concentrations, as part of the endocrine stress response to surgery, may be one factor contributing to the impaired NK cell activity. Peak cortisol concentrations were demonstrated on the day of operation, while the NK cell activity reached its nadir on the first day after operation. However, both *in vivo* and *in vitro* studies have shown that the inhibitory effect of glucocorticoids on the NK cell system is time dependent [24]. Thus, impaired NK cell activity was demonstrated in healthy volunteers as late as 24 h after administration of glucocorticoids [30], while the activity remained unchanged during 5 h of infusion of cortisol [23]. A delayed cortisol effect on the NK cells may therefore explain the findings of the present study.

The decrease in number of circulating NK cells, estimated as Leu 11^+ cells, may be another factor contributing to the impaired NK cell function after operation. The postoperative decline in both activity and number of NK cells are similar to the findings after cardiac surgery [18].

Compared with the NLA group, extradural analgesia reduced cortisol and noradrenaline responses at the end of surgery and this was the only hormonal difference between the two groups. Thus the two different regimens for postoperative analgesia did not influence endocrine responses.

Except for a marked increase in plasma noradrenaline concentration in the NLA group, the catecholamine response to surgery was small in both groups. The results are not in agreement with the study by Engquist and others [31], who found a significant increase in plasma adrenaline and unchanged noradrenaline concentrations after hysterectomy during enflurane anaesthesia, while the addition of extradural analgesia to the enflurane anaesthesia prevented the adrenaline response. However, the general anaesthesia used in the two studies differed, and therefore the results may not be fully comparable.

Surgery during NLA but not extradural analgesia resulted in leucocytosis and an altered balance between the lymphocyte subpopulations with a reduction in the number of T-lymphocytes, T-helper cells, B-lymphocytes and NK cells. These findings are similar to other studies using monoclonal antibodies to monitor lymphocyte subsets after upper urinary tract surgery [32] and cardiac surgery [18].

The effect of extradural analgesia on the distribution of T-lymphocyte subsets was studied by Hole and Bakke [33], who did not find any differences between patients undergoing total hip replacement surgery during general anaesthesia or extradural analgesia. However, neither the type of anaesthesia nor surgery were comparable in these studies, and this may explain the differences.

The combination of anaesthesia and surgery is associated with diminished immunocompetence [1, 2]. However, the contribution of the anaesthetic agents remains controversial. The results of both clinical and *in vitro* investigations have demonstrated that the effect of anaesthesia *per se* on the NK cell system is limited to a reversible, short-term inhibition which appears to be insignificant in relation to the postoperative changes in NK cell activity [34, 35]. In the clinical circumstances of the present study it was not possible to distinguish between the effects of anaesthesia and surgery. Accordingly, the effects of the anaesthetic agents used in the NLA technique on the NK cell system remain to be clarified.

The NK cell system has a key position in the defence against certain microbial infections and growth of tumour cells [6, 8]. In the present study no untoward clinical consequences attributable to the impaired NK cell activity in the NLA group could be demonstrated. Whether the changes in NK cell function induced by general anaesthesia and surgery under certain circumstances increase the susceptibility to postoperative infections or contribute to the dissemination of tumours in patients undergoing cancer surgery remains to be settled.

In summary, we have shown that hysterectomy during NLA is accompanied by impaired NK cell activity and alterations in the composition of circulating lymphocyte subsets. Our findings suggest that the changes result from an interaction between NK cell activity and the endocrine stress response, in which increased serum cortisol may play a major role.

ACKNOWLEDGEMENTS

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SPINAL ANALGESIA WITH HYPERBARIC BUPIVACAINE: INFLUENCE OF AGE

J. P. RACLE, A. BENKHADRA, J. Y. POY AND B. GLEIZAL

SUMMARY

The effects of age were investigated on characteristics of spinal analgesia with hyperbaric bupivacaine in 38 younger patients (< 50 yr: group I), and 48 older patients (> 80 yr: group II). Four millilitre of 0.375% bupivacaine in 2.5% dextrose was injected via the L3–4 space in a lateral position, and the patients were immediately turned supine. In group II, the time to maximum spread was significantly shorter, and the sensory spinal blockade higher (one dermatome) than in group I. The mean sensory recovery of the two uppermost segments did not differ between the two groups. The mean duration of analgesia at the L2 level was increased by only 15 min in the older group. Complete motor blockade of the lower limbs developed most rapidly in group II, while duration of all degrees of motor blockade did not differ significantly with age. Because of great individual variation, the clinical significance of such differences is limited. In the older group, there was a greater decrease in systolic arterial pressure from resting values, despite rapid infusion of lactated Ringer's solution.

In recent years numerous factors have been studied that might influence the characteristics of spinal blockade with hyperbaric bupivacaine. The effects of ageing on spinal analgesia have been investigated only with plain bupivacaine. Cameron and co-workers [1] reported a significant correlation between the extent of sensory block and age, after intrathecal injection of 0.5% bupivacaine 4 ml without glucose. In the study of Pitkänen and others [2] there was a difference between younger (< 50 yr) and older (> 80 yr) patients after spinal anaesthesia with plain 0.5% bupivacaine 3 ml. A significant difference has been reported previously on maximum spread of analgesia between 29 younger (< 50 yr) and 37 older (> 80 yr) patients after subarachnoid injection of 0.5% plain bupivacaine 15 mg [3].

This prospective study was undertaken to compare the characteristics of spinal blockade after injection of hyperbaric bupivacaine 15 mg in a consecutive 6-month period in patients aged less than 50 yr and more than 80 yr.

PATIENTS AND METHODS

Patients

During a six-month period (January–June 1986), all patients aged less than 50 yr and more than 80 yr, and suitable for hyperbaric spinal analgesia, were included in the study; they comprised 39 younger (< 50 yr: group I) and 48 older (> 80 yr: group II) patients undergoing general surgery on the lower trunk or legs (table I). All patients gave informed consent after detailed explanation of the procedure.

Preparation of hyperbaric bupivacaine solution

The plain 0.5% bupivacaine solution has a density of 0.9934 g ml^{-1} at 37 °C, and is relatively isobaric compared with cerebrospinal fluid [4]. Three millilitre of this solution was mixed with 1 ml of 10% dextrose solution to produce a hyperbaric 0.375% solution of bupivacaine in 2.5% dextrose (density: 1.015 g ml^{-1} at 20 °C). All patients received 4 ml of this hyperbaric solution (i.e. bupivacaine 15 mg) which was prepared in a syringe immediately before injection.

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TABLE I. *Mean* (±*SD*) *age, weight, and height of patients in the two groups. Significant differences by Chi-squared test:* *$P < 0.02$. *Significant differences by Student's two-tailed* t *test:* **$P < 0.001$

	Group I (< 50 yr)		Group II (> 80 yr)
Sex (F/M)	12/26	*	28/20
Age (yr)			
Mean	38±11		84±4
Range	19–49		80–95
Weight (kg)			
Mean	73±15	**	59±13
Range	50–117		40–91
Height (cm)			
Mean	169±9	**	162±9
Range	150–190		145–184

Anaesthetic procedure

Flunitrazepam 1–2 mg was given by mouth as premedication 90 min before surgery. Immediately before induction of anaesthesia, an 18-gauge cannula was inserted to an arm vein, and 300 ml of lactated Ringer's solution was infused. The infusion was repeated after injection of the spinal anaesthetic. The patients were placed in a lateral decubitus position, men in the slight head-down position and women slightly head-up, to ensure that the spine was horizontal, on an operating table that was horizontal. Under aseptic conditions, lumbar puncture was performed with a 22- or 25-gauge spinal needle at the L3–4 intervertebral space using either a midline or a paramedian approach. Before injection, a free flow of clear cerebrospinal fluid was ascertained during turning of the needle 90–180° and during aspiration of 0.2 ml. All injections were made at a rate of approximately 1 ml in 4–5 s and all solutions were at room temperature when injected. Immediately after injection, the patient was placed in a supine horizontal position for the duration of surgery.

Arterial pressure and heart rate (sphygmomanometer Dinamap Critikon) were measured at 2.5-min intervals throughout anaesthesia and surgery, and at intervals of 15 min during recovery. ECG was monitored continuously (CM5 configuration) during induction of anaesthesia and during surgery. If systolic arterial pressure (SAP) decreased more than 20 % below resting values, fluid administration was increased. If that was not sufficient (SAP < 20 % but > 30 % during 10 min or more), or if hypotension occurred (SAP < 30 %) [5], ephedrine 15–30 mg was given i.v. (Resting arterial pressure was determined during the anaesthetist's preoperative visit on the day before surgery [6].) When the clinical condition permitted, and with the return of active lower limb movements, the patients were returned to the surgical ward, where they were kept supine for 12 h.

Test procedures

The time of completion of injection of the local anaesthetic solution was used as the base for measurement of all time intervals. The dermatome levels of sensory analgesia were evaluated bilaterally at the mid-clavicular line by pinching with a Pean forceps at 2-min intervals for 30 min. Sensory analgesia was considered complete when the patient did not respond to this forceps closed to its first rachet [7]. When levels of analgesia were not equal bilaterally, the higher was used for statistical purposes. If, during surgery, pain required supplementation with i.v. or inhalation anaesthesia, analgesia was considered unsatisfactory. Patients with unsatisfactory analgesia were not included in the analysis. Motor blockade was assessed at the same time as sensory levels and tested using criteria described by Bromage [8]: 0 = no impairment of movement of legs and feet; 1 = hardly able to flex knees, no impairment of movement of feet; 2 = unable to flex knees, hardly able to move feet; 3 = unable to move feet or knees. Thereafter, analgesia and motor block were assessed every 30 min until analgesia had regressed to the point at which the cutaneous response to clamping in the operative site was identical with that on the forearm, or for a maximum of 5 h after injection. The mean time to recovery from analgesia in the two uppermost segments and the recovery of the L2 segment were noted. Test procedures were performed by two specially trained nurses who were unaware of the nature of the study.

Statistics

All data are presented as means ± standard deviation, together with ranges. Statistical analysis was performed using Wilcoxon rank sum test for ordinal data, Student's two-tailed *t* test for quantitative data and the Chi-squared test for qualitative data. Pearson product–moment correlation coefficients were calculated to show the interrelationships between height of patients, degree of decrease in SAP, and the maximum level of analgesia. A value of $P < 0.05$ was considered statistically significant.

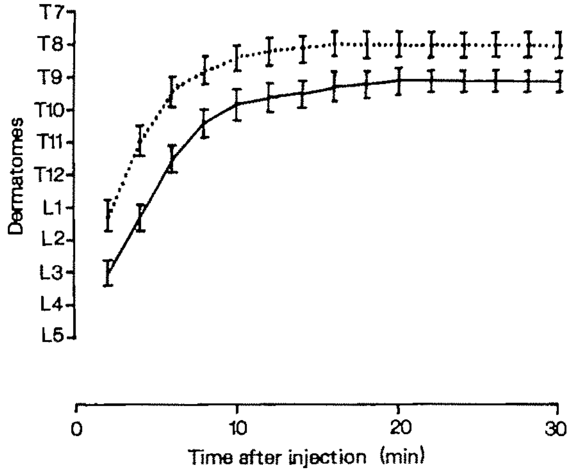

FIG. 1. Mean (±SEM) segmental spread of sensory blockade after spinal analgesia with 4 ml of 0.375% bupivacaine in 2.5% dextrose in 37 patients aged less than 50 yr (●——●) and 48 patients aged 80 yr or more (●····●).

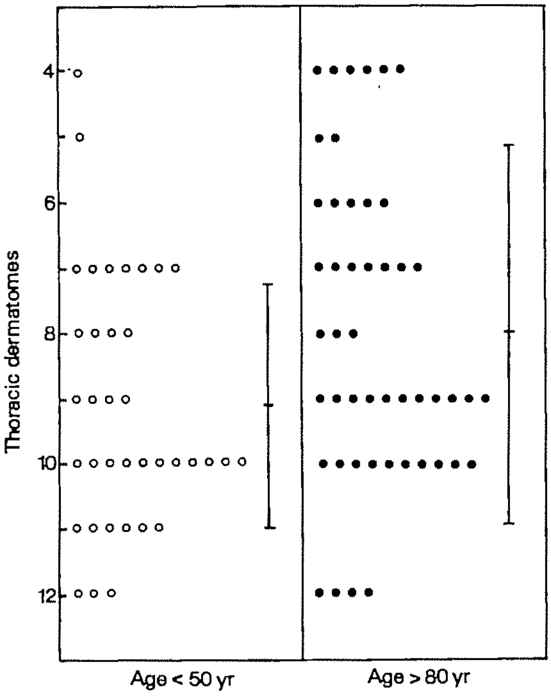

FIG. 2. Maximum level of analgesia indicated by a dot for each patient. The mean block height and standard deviation for each group are indicated by bars ($P < 0.02$).

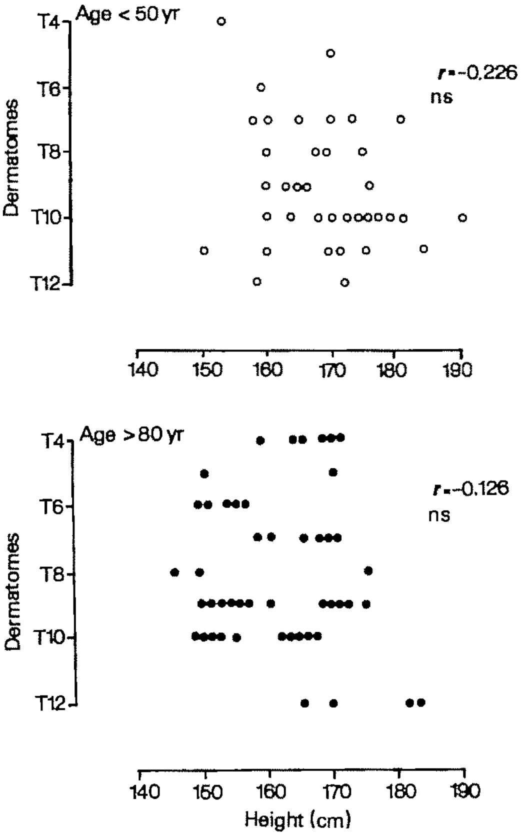

FIG. 3. Scatter plot and linear correlation coefficients (r) of patient's height v. maximum level of analgesia for both groups of patients.

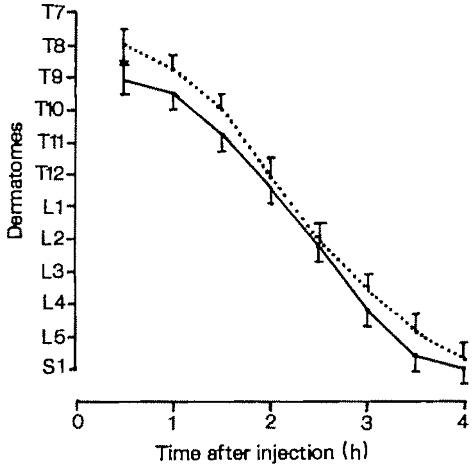

FIG. 4. Mean (±SEM) duration of sensory blockade after spinal analgesia with 4 ml of 0.375% bupivacaine in 2.5% dextrose in 37 patients aged less than 50 yr (●——●) and 48 patients aged 80 yr or more (●····●).

RESULTS

There were more females and fewer males in group II than in group I. Younger patients were heavier and taller than elderly patients (table I). In one patient in group I, general anaesthesia was necessary because of inadequate analgesia, despite apparently successful lumbar puncture. This patient was excluded from analysis.

Mean time from injection to the highest level of sensory analgesia was shorter in group II (8.5 min) than in group I (10.8 min) (fig. 1). The mean maximum level of analgesia (fig. 2) was significantly higher in older (T8) than in younger patients (T9). There was no significant correlation between height of patients and maximum level of analgesia in both groups (fig. 3). The mean time to regression of the level of sensory analgesia by the two uppermost segments did not differ significantly (table II). At the L2 level (fig. 4), a significantly longer duration of action was recorded in group II than in group I (153 min *v.* 138 min).

TABLE II. *Sensory levels of analgesia (mean ± SEM) after intrathecal administration of 4 ml of 0.375% bupivacaine in 2.5% dextrose. Significant differences by Wilcoxon rank sum test:* *P < *0.02*

	Group I (< 50 yr)		Group II (> 80 yr)
Highest level of analgesia			
Mean	T9 ± 1.9	*	T8 ± 2.3
Range	T4–T12		T4–T12
Time from injection to highest level (min)			
Mean	10.8 ± 5	*	8.5 ± 4
Range	4–24		2–20
Time for two-segment regression (min)			
Mean	99 ± 30		97 ± 39
Range	45–180		35–195
Time for regression to L2 (min)			
Mean	138 ± 31	*	153 ± 37
Range	90–210		90–240

TABLE III. *Characteristics of the spinal motor block in the two groups (mean ± SD). Significant differences by Student's two-tailed* t *test:* *P < *0.01*

	Group I (< 50 yr)		Group II (> 80 yr)
Time to onset of total motor block: grade 3 (min)			
Mean	7.8 ± 4	*	5.7 ± 2
Range	2–24		4–10
Duration of grade 3 motor block (min)			
Mean	129 ± 33		132 ± 38
Range	60–180		75–240
Duration of grade 2 motor block (min)			
Mean	155 ± 35		165 ± 37
Range	75–210		105–270
Duration of grade 1 motor block (min)			
Mean	182 ± 30		192 ± 36
Range	135–240		115–300

All patients had complete motor paralysis. Mean onset time to complete motor blockade was significantly shorter in group II than in group I (5.7 min *v.* 7.8 min). Duration of all degrees of motor blockade was not significantly different between age groups (table III).

Mean resting SAP was significantly greater in group II than in group I (table IV). The mean decrease in SAP was 21.6% in patients older than 80 yr and 14.1% in patients younger than 50 yr. The decrease was significant also for mean arterial pressure (MAP) and diastolic arterial pressure (DAP). A linear correlation was found between resting SAP and decrease in SAP in both groups (fig. 5). Decrease in SAP correlated significantly with the maximum level of analgesia only in patients younger than 50 yr (fig. 6). A decrease in SAP of between 20 and 30% persisted for more than 10 min in one (3%) patient in group I, and 11 patients (23%) in group II (table V). A decrease in SAP exceeding 30% was observed in 11 other patients in group II and two patients in group I. The mean volume of lactated Ringer's solution administered during the first 30 min was significantly greater in group II than in group I (table VI). Despite this, 22 (46%) patients in the older group, and three (8%) patients in the younger group were given ephedrine.

DISCUSSION

The younger group in this study comprised more men than women; this reflects personal preference by the patients. The elderly group comprised more females than males as natural mortality is more frequent at this age in men. As care was taken to perform spinal puncture in a strictly horizontal position, the influence of sex seems to have had no direct effect on the distribution of local anaesthetic solution in the cerebrospinal fluid [4].

Hyperbaric bupivacaine was chosen because, in

TABLE IV. *Cardiovascular changes.* (*† From resting values.*) *Significant differences by Student's two-tailed* t *test*: *P < *0.05*; **P < *0.025*; ***P < *0.005*

	Resting values			Maximum variation† (%)		
	Group I (< 50 yr)		Group II (> 80 yr)	Group I (< 50 yr)		Group II (> 80 yr)
SAP (mm Hg)						
Mean ± SD	134 ± 17	**	144 ± 23	−14.1 ± 9.7	***	−21.6 ± 14.1
Range	105–160		100–220	−37.5–0		−50–0
MAP (mm Hg)						
Mean ± SD	98 ± 13		103 ± 15	−13.5 ± 11.1	***	−21.2 ± 14.1
Range	75–120		67–147	−42.7–1		−50.8–0
DAP (mm Hg)						
Mean ± SD	80 ± 11		82 ± 13	−13.8 ± 14.7	*	−21.4 ± 16.7
Range	60–100		50–110	−47.4–6.3		−54.6–0
HR (beat min^{-1})						
Mean ± SD	80 ± 15		85 ± 13	−7.3 ± 18.7		−2.3 ± 21.9
Range	57–110		60–110	−45.5–35.7		−55.6–57.1

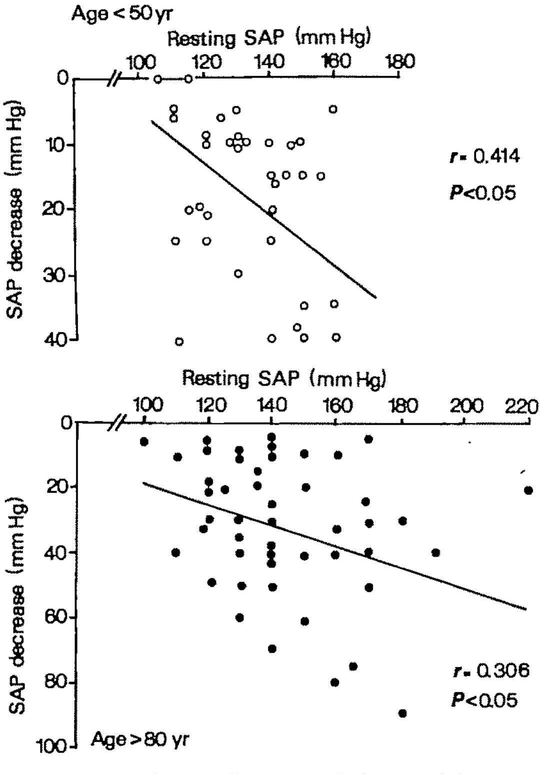

FIG. 5. Scatter plot and linear correlation coefficients (*r*) of resting SAP *v*. SAP decrease for both groups of patients.

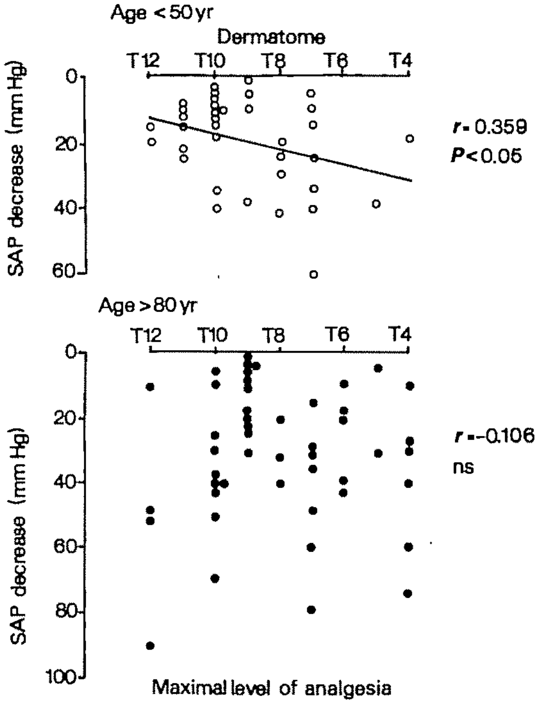

FIG. 6. Scatter plot and linear correlation coefficients (*r*) of maximum level of analgesia *v*. SAP decrease for both groups of patients.

lower trunk surgery (as in repair of inguinal hernia, hysterectomy or prostatectomy), good abdominal muscle relaxation and moderate cephalad level of analgesia are desirable. Previous studies [9–11] had suggested 15 mg as a suitable dose of bupivacaine to obtain a maximum level of analgesia of T7–T10. The solution of bupivacaine used in the present study (0.375 % bupivacaine in 2.5 % dextrose) was not the standard hyperbaric solution (0.5 % bupivacaine solution in 8 % dextrose). Hyperbaric solutions are not commercially available in France, so 10 % dextrose

TABLE V. *Decreases of SAP greater than 20 % from resting values: number of patients (frequency %). Significant differences by Chi-squared test:* *$P < 0.05$; **$P < 0.01$

	Group I (< 50 yr)		Group II (> 80 yr)	Receiving ephedrine?
SAP decrease $> 20\%$ but $< 30\%$ and persistent no more than 10 min	10 (27)		0	No
SAP decrease $> 20\%$ but $< 30\%$ and persistent more than 10 min	1 (3)	**	11 (23)	Yes
SAP decrease $> 30\%$ (hypotension)	2 (5)	*	11 (23)	Yes

TABLE VI. *I.v. fluid and ephedrine administration. Significant differences by Student's* t *test:* *$P < 0.001$; *by Chi-squared test:* **$P < 0.001$

	Group I (< 50 yr)		Group II (> 80 yr)
Volume of lactated Ringer's solution given (ml kg^{-1})			
Mean ± SD	9.7 ± 5.4	*	12.6 ± 4.9
Range	4.3–24.6		6.3–25
Patients receiving ephedrine			
Number	3	**	22
Frequency (%)	8		46

solution is added to plain bupivacaine solution immediately before use. The concentration of dextrose has little effect on the distribution of local anaesthetic solutions within the subarachnoid space when baricity of the solution exceeds 1.0015 [4]. It is possible, however, that a standard solution may behave differently.

Another criticism of the present study might be that all patients received the same dose of bupivacaine (15 mg in 4 ml). However, there was no correlation between height and maximum level of analgesia. No controlled studies have been reported of the effects of the patient's height on the distribution of hyperbaric spinal anaesthetic solution [4].

We observed that sensory analgesia developed more rapidly in the older age group. In this group, the maximum level of analgesia was also higher by a mean of one dermatome. These results are in agreement with studies on the effects of age on spinal anaesthesia with isobaric bupivacaine [1, 3], The relatively similar effects of age on isobaric and hyperbaric spinal anaesthetic solutions are questionable. As age is associated with progressive decrease in cerebrospinal fluid volume, Greene [4] speculated that this might be a determinant in the increasing level of spinal analgesia in elderly subjects. However, as observed by Pitkänen and others [2] with plain bupivacaine solution, a large individual variation has been noted in the spread of analgesia with age. Thus the clinical significance of a difference of only one dermatome in mean maximum level of analgesia is limited. The present study strengthens the view that age plays only a minor role as a predictor of the segmental spread of spinal analgesia.

A difference of only 15 min was observed between the two groups in the recovery of the L2 segment. This small difference was not encountered elsewhere with spinal anaesthesia with plain bupivacaine [2, 3]. The data of Axelsson and co-workers [12] do not support the general hypothesis that an increased duration of anaesthesia with age results from a decrease in systemic absorption of local anaesthetic.

In the present study, the time to attain complete motor block was shorter in the older group. As noted by Pitkänen and others [2], substantial demyelinization in elderly patients may explain the rapidity of total blockade of myelinated A-fibres.

It has long been the clinical impression that systemic hypotension is dependent on the number of dermatomes blocked, but this is only partially true [5]. In young patients, we observed a linear correlation between decrease in SAP and height of blockade, but this was not the case in elderly patients. This suggests that the severity of hypotension varies with the cardiovascular status of the patient. Pitkänen and colleagues [2] found that arterial hypotension was more common in older patients.

Over the age of 65 years, 40–50 % of the population suffer from essential hypertension [13]. We observed that, during spinal anaesthesia, the AP changes were related to the resting AP both in older and younger groups. Structural changes in arterioles of hypertensive patients explain why a similar degree of sympathetic blockade induces greater decreases in AP in the hypertensive than in the normotensive patient [14]. This, may explain our observation of a relationship between resting AP and reduction during spinal anaesthesia, and thus the frequency of hypotension after spinal blockade may not be related solely to age.

In conclusion, the effects of age on spinal analgesia with 0.375% bupivacaine 4 ml in 2.5% dextrose were found to be small. There was a tendency towards increasing height of block, but because of great individual variation, the clinical significance of this finding is limited. In older patients, hypotension was more common, but might not be related solely to age.

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UNPREDICTABILITY OF REGRESSION OF ANALGESIA DURING THE CONTINUOUS POSTOPERATIVE EXTRADURAL INFUSION OF BUPIVACAINE

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SUMMARY

Twenty-four otherwise healthy patients scheduled for elective major abdominal surgery received general anaesthesia plus lumbar extradural analgesia. A loading dose of 0.5% plain bupivacaine was given to produce sensory analgesia (pin prick) from T4 to S5 and followed by a continuous infusion of 0.5% plain bupivacaine 8 ml h^{-1}*. Pain, scored on a 5-point scale, and sensory analgesia were assessed hourly for 16 h after skin incision. If sensory analgesia decreased by more than 5 segments from its preoperative level, or if the pain score reached 2 (moderate pain), the patients were removed from the study, and pain was treated otherwise. Only three patients maintained their initial levels of sensory analgesia and a pain score of less than 2. In the remaining patients sensory analgesia decreased at least 5 segments or pain score reached 2 between 4 and 16 h after skin incision. We found a weak correlation between increasing age and the duration of sensory analgesia ($r = 0.46$, $P < 0.05$), but no significant correlations between duration of sensory analgesia and sex, weight, height, body surface area, serum albumin concentration, duration or site of operation.*

Extradural blockade with local anaesthetics, in combination with light general anaesthesia, relieves pain during major abdominal surgery. However, the maintenance of the same degree of sensory analgesia (and pain relief) during the postoperative period is difficult as a result of tachyphylaxis [1–5] or other factors [6, 7]. However, in those studies, extradural analgesia was maintained by the administration of "top up" doses, or by continuous infusion using a variable dose rate, thereby hindering the interpretation of those factors important to the maintenance of a defined level of sensory analgesia. The purpose of this study was to investigate the possible correlations between age, sex, weight, height, body surface area, serum albumin concentration, duration of surgery and site of operation and sensory analgesia during a standardized regimen utilizing a continuous extradural infusion of bupivacaine, in order to assess the possible predictive value of these clinical data in relation to the duration of sensory analgesia.

PATIENTS AND METHODS

Twenty-four patients scheduled for elective major abdominal surgery were premedicated with diazepam 0.2 mg kg^{-1} and general anaesthesia was induced with thiopentone 3–5 mg kg^{-1}; after precurarization with pancuronium 0.01 mg kg^{-1}, suxamethonium 1.5 mg kg^{-1} was used to facilitate orotracheal intubation. General anaesthesia was maintained with 0.25–0.75 % halothane and 67 % nitrous oxide in oxygen. Before the induction of general anaesthesia, an extradural catheter was inserted between L2 and L3 or L3 and L4 and 0.5 % plain bupivacaine was used to produce a sensory blockade from T4 to S5. Immediately thereafter, 0.5 % plain bupivacaine was delivered by an infusion pump at a fixed dose rate (8 ml h^{-1}), and scheduled to continue for 16 h after skin incision. The following clinical data were recorded: age, sex, height, weight, body

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surface area, duration of operation and whether surgery was in the upper or lower abdomen. Upper abdominal surgery was defined as a procedure involving an assumed afferent innervation to the coeliac or superior mesenteric plexus, and lower abdominal surgery as a procedure involving innervation to the inferior mesenteric plexus.

Upper procedures were: right hemicolectomy ($n = 3$), exploratory laparotomy ($n = 3$) antrectomy ($n = 3$), small bowel resection ($n = 2$), pancreatico–gastrostomy ($n = 1$), cholecystectomy ($n = 1$) and gastrectomy ($n = 1$).

Procedures involving the lower abdomen were: low anterior resection ($n = 5$), colo–anal anastomosis ($n = 2$) abdomino–perineal exision of rectum ($n = 1$), cystectomy ($n = 1$) and sigmoid resection ($n = 1$).

Pain scores on a 5-point scale (no pain, slight pain, moderate pain, severe pain and unbearable pain) and the levels of sensory analgesia (pin prick, bilateral) were assessed hourly after the patients recovered from general anaesthesia. If the rostrad level of sensory analgesia decreased by more than 5 segments from the preoperative level, or if the pain score reached 2 (moderate pain), the patient was removed from the study and pain was treated by other methods.

Informed consent was obtained from all patients.

Data were analysed using Student's t test for unpaired data and the method of least squares for calculation of linear regressions. Multiple linear regression was computed by NWA Statpak program. P values less than 0.05 were considered significant.

RESULTS

The preoperative level of sensory analgesia was T3.8 ± 0.5 (mean ± SEM) after a loading dose of 0.5% bupivacaine 24 ± 0.5 ml.

Only three patients maintained a stable level of sensory analgesia and a pain score below 2 during the 16-h observation period (small bowel resection ($n = 1$), colo–anal anastomosis ($n = 1$) and sigmoid resection ($n = 1$)). Regression of sensory analgesia always corresponded with an increase in pain score, and no patient showed a pain score ≥ 2 without a simultaneous decrease in the level of sensory analgesia to below that of the skin incision (figs 1, 2).

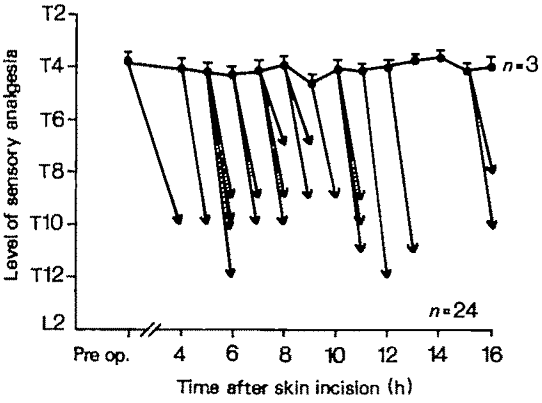

Fig. 1. Changes (mean ± SEM) in levels of sensory analgesia during continuous extradural infusion of 0.5% bupivacaine 8 ml h^{-1} after abdominal surgery.

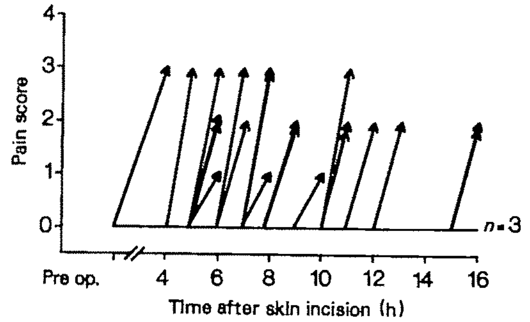

Fig. 2. Changes in pain score (0–4) during continuous extradural infusion of 0.5% bupivacaine 8 ml h^{-1} after abdominal surgery.

The relationships between the duration of sensory analgesia, defined as time until a decay > 5 segments or pain score ≥ 2 from initial level, and age, sex, weight, height, body surface area, serum albumin concentration, duration of surgery and site of surgery are shown in figure 3. There was a weak correlation between age and duration of sensory analgesia ($r = 0.46$, $P < 0.05$), but there were no significant correlations between the duration of sensory analgesia and sex, height, weight, body surface area, serum albumin concentration, and duration of surgery or site of operation. By multiple linear regression analysis our results did not suggest that the duration of sensory analgesia could be predicted, since no significant scoring system could be obtained ($F = 1.171$; $P > 0.05$.)

There was no difference > 1 segment in bilateral spread of sensory analgesia.

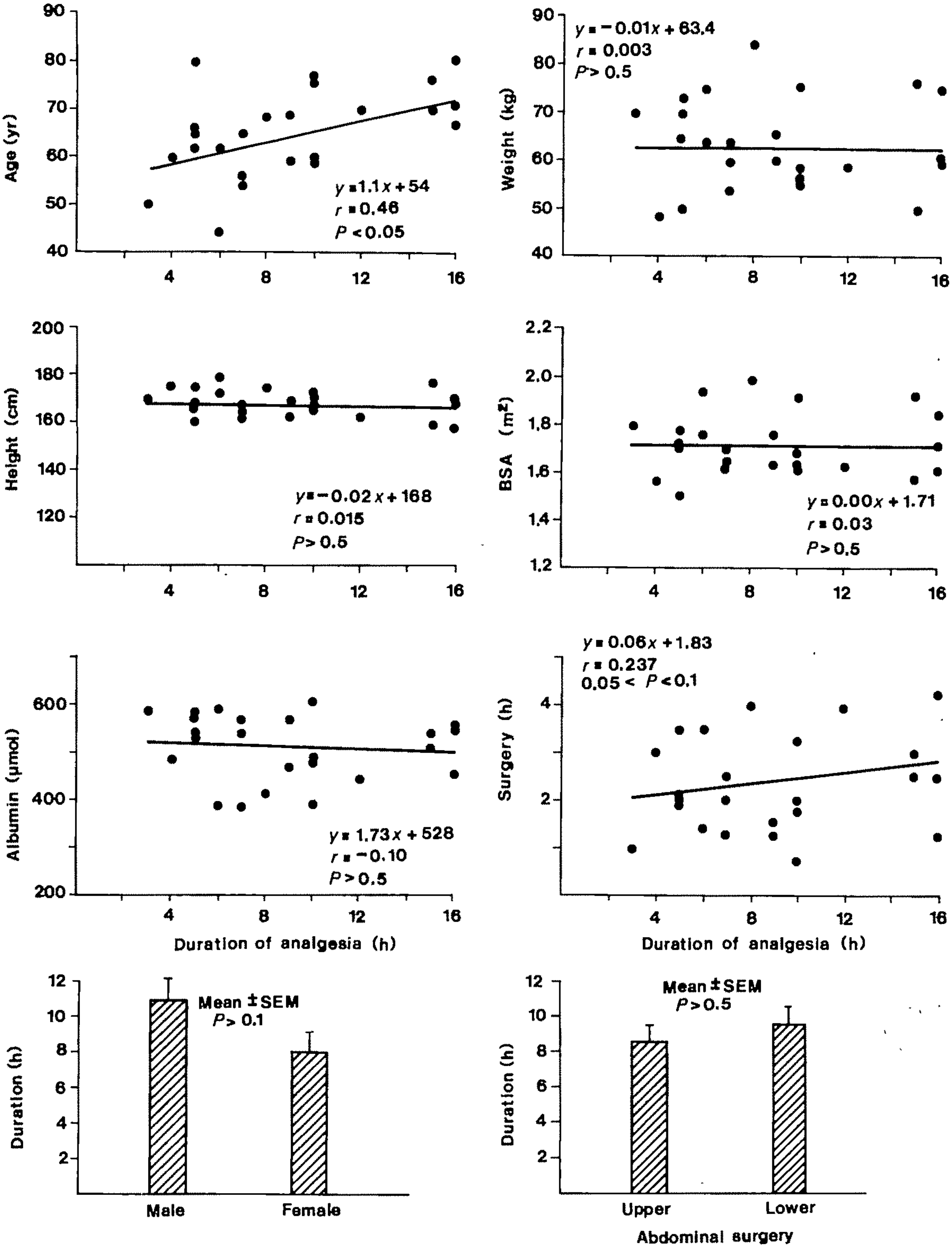

FIG. 3. Relationships between age, weight, height, body surface area (BSA), serum albumin concentration, duration of surgery, sex or site of surgery, and duration of sensory analgesia during the continuous extradural infusion of 0.5% bupivacaine 8 ml h^{-1} after abdominal surgery.

DISCUSSION

Extradural analgesia with local anaesthetics is effective in preventing intraoperative pain and may be useful in the alleviation of pain in the postoperative period. However, several problems have been described during the maintenance of analgesia using so-called continuous techniques of extradural blockade with local anaesthetics.

Tachyphylaxis has been reported during intermittent extradural injections [1], as well as during continuous extradural infusion [2,3,5], but the explanation of the tachyphylaxis remains unknown [7]. Furthermore, an unpredictable instability of sensory blockade, which could not be explained by tachyphylaxis, has been reported during the prolonged but intermittent extradural administration of local anaesthetics in the postoperative period [6,8]. The explanation of the variability in sensory analgesia in these latter studies may be changes in the compliance of the extradural space or in the position of the catheter.

In our study we found a weak correlation between age and time before regression of sensory analgesia in the postoperative period. Bromage, Pettigrew and Corwell [1] demonstrated a correlation between age and segment-minute analgesia to the initial dose of local anaesthetic, but others have failed to demonstrate any relationship between dose and maximum extent of analgesia [9]. No comparative studies are available between intermittent and continuous extradural analgesia using a constant administration regimen.

Renck and colleagues [2] used a continuous low-volume administration of 1% bupivacaine and found no relationship between the segmental spread of analgesia and dose, or between dose per segment blocked and age, sex, height or weight of the patient in thoracic extradural analgesia. However, in that study "top up" doses were administered when the patients complained of pain, thereby hindering interpretation. Ross, Clarke and Armitage [10] used a high volume–low concentration of bupivacaine (0.125%, 20 ml h^{-1}), but adjusted the infusion rate when necessary, again hindering any interpretation of those factors of possible significance in regard to the maintenance of sensory analgesia. It may be argued that the infusion of bupivacaine to the lumbar extradural space in a rather low volume (8 ml h^{-1}) will, not surprisingly, result in regression of analgesia when the initial level of sensory analgesia is as high as T3.8—as in the present study. However, despite its relevance, this argument does not explain away our main findings of a pronounced and unpredictable variability of regression of analgesia during a constant infusion regimen.

We have described an enhancing effect of systemic morphine on the extent of sensory analgesia during the continuous extradural infusion of bupivacaine in the postoperative period [11]. This study may suggest that the local anaesthetic solution is apparently present at higher levels, but that other factors may reduce its effect with time. Since morphine may re-establish the extent of the sensory block, changes in the distribution of local anaesthetics in the extradural space are probably not of any or are of only minor importance as far as the regression of sensory analgesia is concerned. This is further supported by a recent study in which the addition of morphine to the extradural space prevented any decay of postoperative sensory analgesia during a continuous extradural infusion of bupivacaine [12].

The explanation of the decrease in sensory analgesia and the augmenting effect of extradural or systemic morphine on sensory analgesia during the continuous extradural infusion of bupivacaine may be found in recent studies on the anatomy and physiology of afferent nociceptive traffic. Thus the decrease in sensory analgesia, as seen in this study, may be explained by a relative increase in afferent input, since an experimental study has demonstrated an increase in nociceptor excitability both peripherally and in the spinal cord, following peripheral trauma [13]. Unfortunately, no information is available on the duration of sensory analgesia during the continuous extradural infusion of bupivacaine in patients without trauma. However, another explanation for the regression of analgesia may be that changes occur in the concentration of bupivacaine as a result of alterations in systemic uptake from the extradural space. This point requires further evaluation.

In conclusion, the difficulties in maintaining a high and constant level of sensory analgesia and total postoperative pain relief during the continuous infusion of a fixed dose of bupivacaine remain unexplained. Our results suggest that sex, weight, height, body surface area, serum albumin concentration and the duration and site of the operation are unimportant in this context. Old age may, to a minor degree, facilitate the maintenance of sensory analgesia, at least during the infusion regimen described in this study.

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COMPARISON OF THE RECOVERY CHARACTERISTICS OF DIAZEPAM AND MIDAZOLAM

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Midazolam has a useful role as a premedicant, a sedative for minor surgical procedures and an induction agent. In comparison with diazepam in propylene glycol, the water-soluble midazolam produces a lower incidence of pain on injection and of thrombophlebitis [1], and has advantageous physicochemical and pharmacokinetic properties [2]. Although it has the shortest elimination half-life of all the commercially available benzodiazepines, clinical studies suggest that the recovery from equipotent doses of midazolam and diazepam is comparable [3–6]. The purpose of this study was to compare the efficacy and recovery characteristics of midazolam and diazepam following the administration of equipotent doses of each drug.

SUMMARY

A double-blind crossover comparison of efficacy and recovery from midazolam 5 mg and diazepam (in propylene glycol) 10 mg was undertaken in eight volunteer subjects. It was found that midazolam was significantly more potent in this dose ratio than diazepam, helping to explain the finding of previous studies that the recovery from midazolam and diazepam in a 1:2 dose ratio is comparable.

SUBJECTS, MATERIALS AND METHODS

Eight male volunteers in the age range 22–28 yr (mean 25 ± SD 3 yr; weight 75 ± 11 kg; height 182 ± 9 cm) were selected. All were healthy, were not receiving any psychotropic drugs and had been asked to refrain from ingesting alcohol for 24 h, or coffee for 6 h, before the study period.

On each of two study days an 18-gauge cannula was inserted to a vein in the right antecubital fossa and physiological saline was infused at a constant rate. The volunteers then received diazepam in propylene glycol (Valium, Roche) 10 mg i.v., or midazolam (Hypnovel, Roche) 5 mg i.v. according to a random order crossover design. The midazolam was diluted in physiological saline to the same volume (2 ml) as the diazepam by an independent technician and injected by an anaesthetist not involved with data collection. Injections were given into the saline infusion and were made double-blind for the volunteer and observer by masking both syringe and i.v. tubing. Each study was separated by an interval of at least 3 weeks and was performed in the same environment controlled for temperature and light intensity with the same observer performing the tests of recovery and sedation.

A battery of psychomotor/sedation tests (see below) was performed by each subject before, and at 10, 30, 60, 120 and 180 min after, injection.

During the first 10 min after injection, sedation was assessed by the observer using a seven-point scoring system (table I), each change in score being recorded on a small microcomputer system with timing function. This observer assessment was chosen because psychomotor tests could not be performed because of the degree of sedation.

To examine long-term memory, a series of simple line diagrams were shown to the subjects for 20 s before, and at 1, 5, 10, 20 and 30 min after, drug administration. Recall was tested at 24 h.

Heart rate, arterial pressure (Dinamap), rate of ventilation, end-tidal carbon dioxide concentration (nasal cannulae with Datex CO_2 analyser) and oxygen saturation (Biox ear oximetry) were recorded during the first 30 min of the study period.

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TABLE I. *Sedation scale*

0 = No subjective or objective sedative effects
1 = Onset of first observable drug effect
2 = Drowsy, partial lid closure
3 = Upper lid bisects pupil or full lid closure. Responds to verbal command
4 = Unresponsive to verbal command, responds to mild physical stimulus
5 = Responsive only to painful stimulus (trapezius squeeze)
6 = Unresponsive

Psychomotor/sedation tests

Five simple assessments were chosen to encompass a range of benzodiazepine effects, relevant to the clinical recovery of function: subjective sedation, cognition, short term memory and visuo-motor performance.

Visual analogue sedation scale—a subjective measure of perceived sedation. Subjects were asked to assess their degree of sedation by marking a 10-cm linear visual analogue scale (VAS). The extremes were denoted "wide awake, alert" and "drowsy, dull."

Letter deletion test. Thirty lines of 25 randomly typed upper and lower case letters were given and subjects deleted as many letters *g* or *G* as possible in a 2-min interval. This form of simple pen and paper test is sensitive to the effects of benzodiazepines and is an adaption of that described by Dixon and Thornton [9]. The letter *g*/*G* was chosen because of the dissimilarity between the upper and lower case characters. This test has a saccadic eye movement component in addition to motor co-ordination and cognition.

Simple Reflex Time—a robust measure of sensory-motor performance [10]. Reflex time was assessed as the time taken to press a button after a visual light stimulus. The mean reflex time was taken as the averaged value for the last 30 of 35 attempts.

Simple addition. A cognitive task in which 25 pairs of two-digit numbers were given for addition, each requiring an answer to be given within a 5-s interval onto a microcomputer keyboard.

Seven-digit recall—a test of short term memory. Thirty consecutive seven-digit numbers were presented on a microcomputer screen for recall. Each number was shown to the subject for 4 s, and after a 7-s interval subjects entered the memorized number onto the keyboard.

Reflex time, simple arithmetic and seven-digit recall were each performed on an Apple 11e microcomputer.

Statistical analysis

t Tests were used for parametric comparisons and Chi-square tests for non-parametric comparisons, where appropriate. A Wilcoxon Signed Rank test was used to analyse the between-group differences in sedation score during the first 10 min, by comparing for each subject and drug the area under the curve of the sedation-time plot.

The changes in the psychomotor/sedation test battery were analysed as a whole using a multivariate analysis of variance [7] with treatment, time, subject and interaction terms. Tests of significance of effects were made with the Lawley-Hotelling trace statistic. As there were significant treatment-time and treatment-subject interactions, the treatments were compared at each time and for each subject using canonical variates analysis. Comparisons were made using the Bonferroni inequality to give an experimental level of significance less than or equal to 0.05 [8].

TABLE II. *Mean change in physiological variables from preinjection value. M = Midazolam, D = diazepam*

	1 min		3 min		5 min		10 min	
	M	D	M	D	M	D	M	D
Heart rate (beat min^{-1})	9	8	7	4	4	5	2	6
Systolic pressure (mm Hg)	−6	3	−11	−2	−13	−4	−13	−9
Diastolic pressure (mm Hg)	1	5	−1	2	−7	−4	−8	−8
Ventilatory rate (b.p.m.)	9	8	7	4	4	5	2	6
E'_{CO_2} (%)	0.1	−0.1	0.1	0	0.1	0.1	0	0

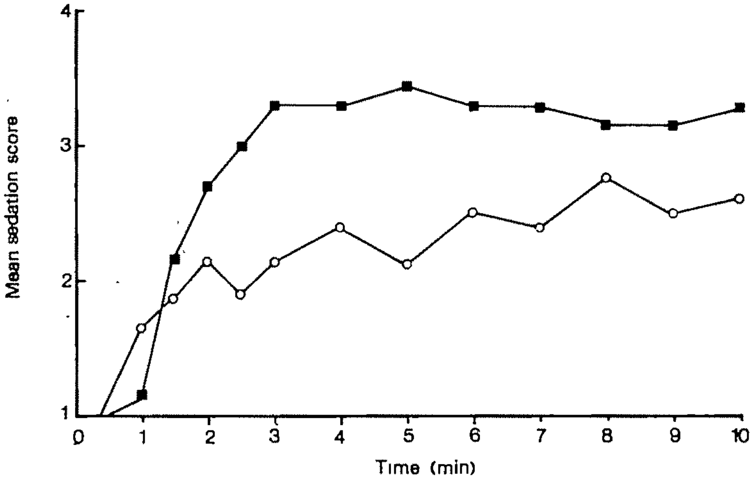

FIG. 1. Mean sedation score (table I) for 10 min following drug injection. ○ = Diazepam; ■ = midazolam.

RESULTS

After the injection of the relevant drugs there were no significant between-group differences in heart rate, arterial pressure, ventilatory rate, end-tidal carbon dioxide concentration or oxygen saturation. Mean changes are shown in table II.

The mean times to onset of drug effect did not differ significantly (diazepam 28 ± SD 15, midazolam 32 ± SD 22 s).

During the first 10 min the observed degree of sedation was found to be significantly greater with midazolam ($P < 0.05$) (fig. 1). Similarly, as assessed by the psychomotor tests, recovery was better in the diazepam group at 10 ($P < 0.0001$),

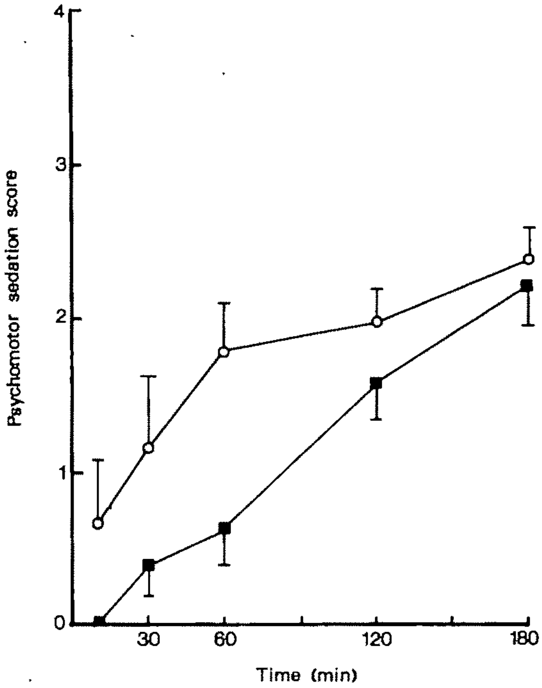

FIG. 2. Psychomotor/sedation test score. Mean (±SEM) number of tests returning to the preinjection baseline score. ○ = Diazepam; ■ = midazolam.

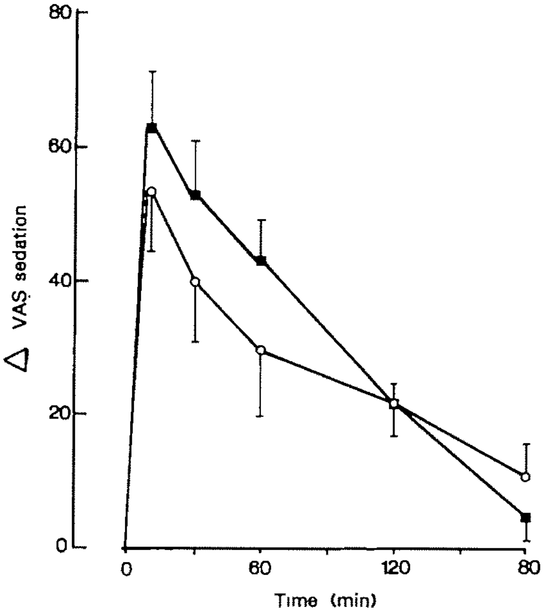

FIG. 3. Mean change in the subjective visual analogue scale for sedation from the preinjection baseline. ○ = Diazepam; ■ = midazolam.

30 ($P < 0.0001$) and 60 min ($P = 0.001$). This trend was consistent for all subjects at these times. At 180 min the midazolam group performed slightly better than the diazepam group (ns). Figure 2 is a summary of the psychomotor test battery, representing the mean number of the five tests that had returned to the control values at the given time. The mean change in the visual analogue sedation score is shown in figure 3.

Amnesia for picture recall, analysed for the complete 30-min test period, was significantly greater in the midazolam group ($P < 0.01$).

DISCUSSION

The potency of midazolam relative to diazepam has been estimated to be 1.5–2.1:1 [11] and several clinical studies of diazepam with midazolam in this dose ratio have found the recovery characteristics to be comparable. In a study of dental sedation with subjects who received a mean dose of diazepam 26 mg or midazolam 13 mg, Skelly and colleagues [3] found no difference between the groups when six psychomotor tests were used to assess recovery. Whitwam, Al-Khudairi and McCloy [12] found similar recovery characteristics in gastroscopy patients who received diazepam 0.15 mg kg^{-1} or midazolam 0.07 mg kg^{-1}, but noted that the midazolam group were more sedated on arrival in the recovery room and had a greater degree of amnesia.

The apparent discrepancy between the recovery and pharmacokinetic characteristics of midazolam and diazepam has been attributed to the presence of active metabolites [5] and to their similar distribution half-lives [13].

It is unlikely, however, that the principal active metabolite of midazolam, alpha hydroxy midazolam, plays an important part in delaying recovery as its own elimination half-life (< 1 h) is considerably shorter than that of the parent drug [14]. Alpha hydroxy midazolam probably exerts its most significant clinical effect after oral administration of midazolam (because of the high first-pass effect) when it potentiates rather than prolongs the action of midazolam [15].

Although midazolam is classified as a short-acting benzodiazepine, on the basis of its elimination half-life, it is the distribution half-life which determines initial recovery. The distribution half-life of diazepam is 0.3 h (SD 0.1 h) [16], comparable to some values found for midazolam (0.31 h (SD 0.08 h) [17]).

Our results indicate that midazolam 5 mg is significantly more potent than diazepam 10 mg, in terms of both subjects' and investigators' assessments of sedation, amnesia and objective psychomotor testing. However, by 3 h this effect showed signs of reversal, with the results in the midazolam group beginning to improve beyond those of the diazepam group.

We believe, therefore, that the doses used in our study were not equipotent, and that the relative potency of the two drugs is significantly greater than 2:1 (perhaps nearer 3:1). This would help explain the findings of those other studies which demonstrated that midazolam has a similar recovery and more intense amnesia than that of diazepam. If the newer formulations of diazepam (mixed micelle or lipid emulsion) were to be compared with midazolam, the discrepancy between their relative potencies are likely to be even greater [18].

In summary, midazolam 5 mg was found to be significantly more potent than diazepam (in propylene glycol) 10 mg and to be associated with delay in recovery. Our results indicate that comparisons of recovery from the two drugs should not be made with a dose ratio of 2:1 and that the advantageous pharmacokinetic profile of midazolam may be apparent only if its considerably greater potency is taken into account.

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VISUAL EVOKED POTENTIALS AND CHANGES IN SERUM GLYCINE CONCENTRATION DURING TRANSURETHRAL RESECTION OF THE PROSTATE

W. F. CASEY, V. HANNON, A. CUNNINGHAM AND J. HEANEY

SUMMARY

Visual evoked potentials were recorded in 10 patients undergoing transurethral prostatectomy under subarachnoid anaesthesia. They were compared with those obtained in a control group (n = 5) having other operative procedures also under spinal anaesthesia. Serum concentrations of glycine, ammonia, glucose and sodium, and osmolality, were determined during the perioperative period. The prostatectomy group demonstrated a significant prolongation of visual evoked potential P_2 latency in the postoperative period when compared with preoperative values ($P < 0.01$). No significant changes in latency occurred in the control group when measured at similar times. The prostatectomy group demonstrated a significant increase in serum glycine concentration ($P < 0.01$); changes in serum ammonia and sodium concentrations and osmolality were not significant. There was no correlation between visual evoked potential latency and changes in serum glycine concentration. Changes in visual evoked potential during transurethral prostatectomy may be the result of an accumulation of a metabolite of glycine.

The excessive absorption of irrigating fluid during transurethral prostatectomy may result in changes in haemodynamic variables and disturbances of neurological function [1–4]. The cardiovascular changes are the result of an increase in intravascular volume, and may lead to arterial hypertension, increased myocardial work and congestive heart failure. Numerous disturbances of neurological function have been reported—such as irritability, coma, seizures and alterations in vision (transient blindness, blurred vision and pupillary dilatation).

Initially, distilled water was used as the irrigating fluid because it provided the least optical impairment; however, it caused haemolysis of red blood cells [1,5]. Electrolyte solutions are unacceptable because they cause dispersion of the electrical current of the resectoscope. Glycine 1.5% is popular as an irrigating fluid because it is iso-osmolar with blood, non-electrolytic, relatively inexpensive and because its transparency affords good optical conditions. Intravascular absorption of irrigating fluid during prostatic resection depends on the number of open venous sinuses, the duration of resection and the hydrostatic pressure used. It has been estimated that 10–30 ml of fluid is absorbed for every 1 min of resection time [6].

Sensory evoked potentials are electrophysiological responses of the nervous system to sensory stimuli. Visual evoked potentials (VEP) reflect the functional integrity of the eye and the optic tracts [7, 8] and are a sensitive index of abnormalities in the retina and optic pathways. They are also affected by CNS depressant drugs (including general anaesthetics), and changes in temperature and haematocrit [7–11]. Diminished visual acuity to at least 20/100 does not affect the P_2 latency [12]. Increases in the concentrations of serum glycine or its metabolite (ammonia) have been implicated in the aetiology of visual disturbances and encephalopathy following transurethral resection of the prostate (TURP) [2,13,14]. In dogs, the infusion of glycine was shown to cause

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alterations in VEP wave forms [15], but this has not been confirmed during TURP in man.

The present study was designed to investigate the effect of irrigation with glycine (during TURP) on visual evoked potentials, to assess the systemic absorption and hepatic metabolism of glycine during TURP, and to note any correlations between the changes in VEP and those in the concentrations of glycine and ammonia.

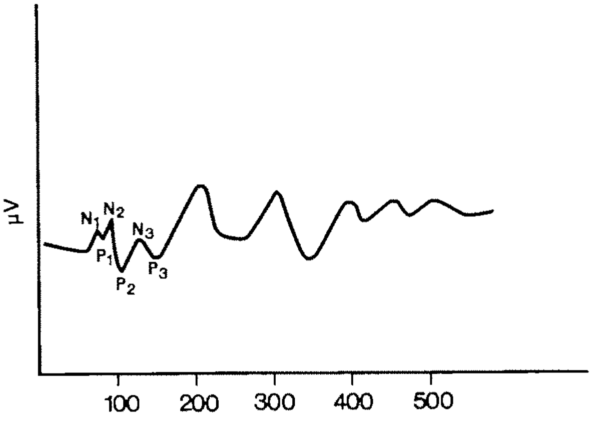

FIG. 1. Normal VEP recording in an awake adult.

PATIENTS AND METHODS

Appropriate institutional and patient approval was given for the study. Ten patients undergoing elective TURP under subarachnoid anaesthesia, and in whom 1.5% glycine was used as the irrigating fluid, were studied. Five patients undergoing other operative procedures under subarachnoid anaesthesia served as a control group. Patients suffering from disorders of the eye or the central nervous system or receiving medication known to affect VEP were excluded from the study [7, 8].

No premedication was administered. Under local anaesthesia, a 16-gauge cannula was placed in a peripheral vein and a 22-gauge cannula placed in a radial artery. An infusion of physiological saline solution was commenced. Arterial pressure, the electrocardiogram and temperature were recorded during the perioperative period. Oral temperature was recorded using a mercury thermometer before operation, and at 45, 75 and 120 min following the start of the resection. Visual evoked potentials were recorded from bipolar scalp electrodes in the 0_Z and C_Z position with the right forehead used as the ground electrode [16]. The patients were positioned in the Fowler position. The visual stimulus, a shift (reversal) of a checkerboard pattern, was placed 1.5 m in front of the patient. The squares reversed colour (without changing total light output (luminence) [8]) 128 times at a rate of 1.1 times per second. The brain electrical activity was recorded after each stimulus and averaged to form the VEP. Visual evoked potentials were obtained using a single purpose computer (Medelec NS6 Modular Electromyographic System). The occipital VEP generally consists of five or more deflections designated, according to their direction, P (positive—downstroke deflection) or N (negative—upstroke deflection (fig. 1). In VEP recordings amplitude (voltage) and latency (time) are measured. Latency (stimulus to peak) was measured using the P_2 (P100) wave, which normally occurs 100 ms after the pattern shift stimulus, hence its name. The P_2 wave is the peak normally used to measure changes in latency using pattern shift stimulus [8]. Changes in amplitude were not recorded in this study as they are thought to be less reliable than those in latency [8]. The changes in latency of the P_2 peak were measured using the cursor on the computer oscilloscope display (filter settings: 0.32–80 Hz, sensitivity 20 μV; electrical activity was recorded for 200 ms). Further information with respect to the methods may be obtained from the literature [17,18].

Visual evoked potentials were recorded before resection, and 15 min and 120 min following the start of resection. At least three individual VEP waveforms were recorded at each period of recording. Blood samples were obtained before resection, and every 15 min thereafter for 120 min, and the serum sodium, glucose, glycine and ammonia concentrations, and osmolality, measured. Haematocrit (serum) was also measured in the postoperative period.

Under aseptic conditions, subarachnoid anaesthesia was performed with the administration of hypobaric 0.5% bupivacaine 2.5–3.5 ml without adrenaline, through a 25-gauge needle placed in the subarachnoid space at the L3–4 space to achieve regional blockade to a level of T10. The volume of irrigating fluid used and the volume of washout fluid were measured and the volume absorbed calculated.

Data were analysed using Wilcoxon Sign Ranking and linear regression coefficients. $P < 0.01$

was considered statistically significant. Results are presented as mean ± standard error of mean.

RESULTS

The mean weight and age were similar in both groups; however, the duration of surgery was significantly longer in the control group (table I). Mean weight of gland resected was 21 ± 5.23 g and mean volume of fluid absorbed was 1518.2 ± 411.3 ml. Serum haematocrits when measured 15 min after the end of resection were all greater than 35%.

The major finding was a statistically significant prolongation of the latency of the postoperative P_2 peaks in the glycine group when compared with the preoperative value ($P < 0.01$) (fig. 2). The latency increased from 112 ± 5.6 ms before operation to 130 ± 3.5 ms 15 min and 122 ± 3.6 ms 120 min after the start of the resection. Changes in latency of other peaks were not measured. No significant changes occurred in the control group when measured at similar times. Alterations in cardiovascular variables and temperature were similar in both groups (fig. 3).

Figure 4 shows a typical VEP wave form in a patient undergoing transurethral prostatectomy. It shows that the P_2 peak latency became prolonged at 15 min and that, although returning to baseline values at 120 min, it was still increased in relation to the preoperative value.

TABLE I. *Demographic data (mean ± SEM) of the glycine and control groups*

	Glycine group	Control group
Age (yr)	70.9 ± 1.622	67.0 ± 5.2
Weight (kg)	69.0 ± 2.23	72.1 ± 3.4
Duration of operation (min)	38.0 ± 5.73	60.0 ± 5.6
Mean weight of gland (g)	21.0 ± 5.23	
Mean volume of fluid absorbed (ml)	1518.2 ± 411.3	
Post-op. Hct (%)	37.9 ± 1.21	

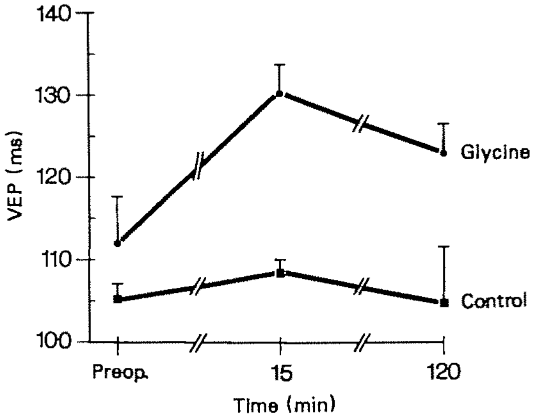

FIG. 2. Changes in mean VEP latency in the glycine and control groups. Significant prolongation of VEP latency occurred in the glycine group in the postoperative period when compared with preoperative value ($P < 0.01$).

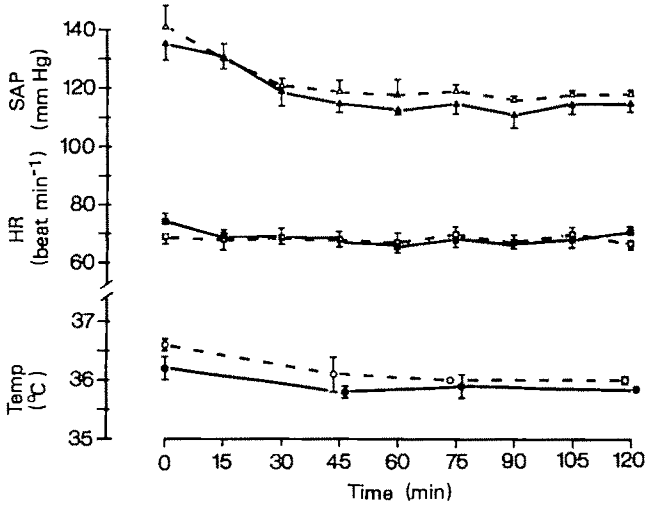

FIG. 3. Haemodynamic variables and temperature in glycine (continuous lines) and control (dashed lines) groups. HR = heart rate; SAP = systolic arterial pressure.

Serum glycine concentration showed a threefold increase at 15 min with the maximum increase at 45 min (fig. 5). The increases in concentration were significant ($P < 0.01$). Although increases in serum ammonia concentration occurred (maximum values at 45 and 105 min), these were not significant. Dilutional hyponatraemia and hypo-osmolality did not develop during the perioperative period.

Although there were significant increases in VEP latency and serum glycine concentration, no correlation could be found between the changes in VEP and serum glycine concentration.

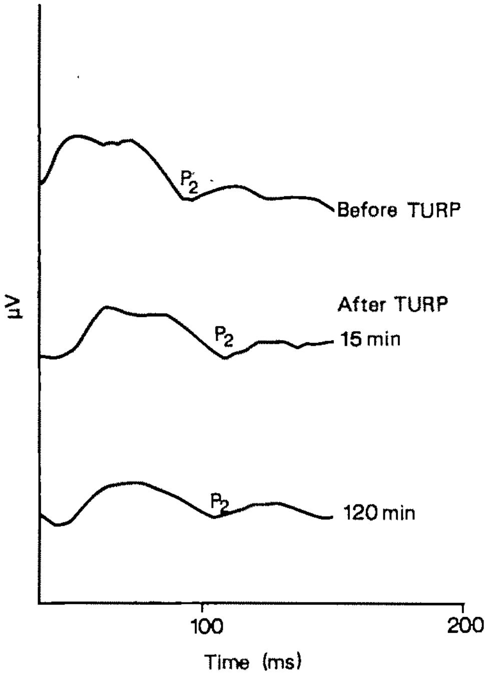

FIG. 4. Representative VEP recorded from a patient undergoing TURP obtained before resection, and 15 and 120 min after resection.

DISCUSSION

TURP has been associated with neurological disturbances and these have been attributed to hyponatraemia, hypo-osmolality and toxicity from the systemic absorption of glycine or its metabolite (ammonia) [1, 13, 14]. Transient visual disturbances, following TURP, were found in association with high serum glycine concentrations [2]. Visual evoked potentials are a very sensitive index of the function of the eye and the optic pathways and, although none of the patients complained of any gross visual disturbances, all had prolongation of P_2 latency in the postoperative period. In the glycine group temperature decreased by 0.6 °C compared with 0.4 °C in the control group. However, this change in temperature was insufficient to cause a prolongation of latency of 20 ms [10]. Serum haematocrit in the glycine group was greater than 35 % in all patients

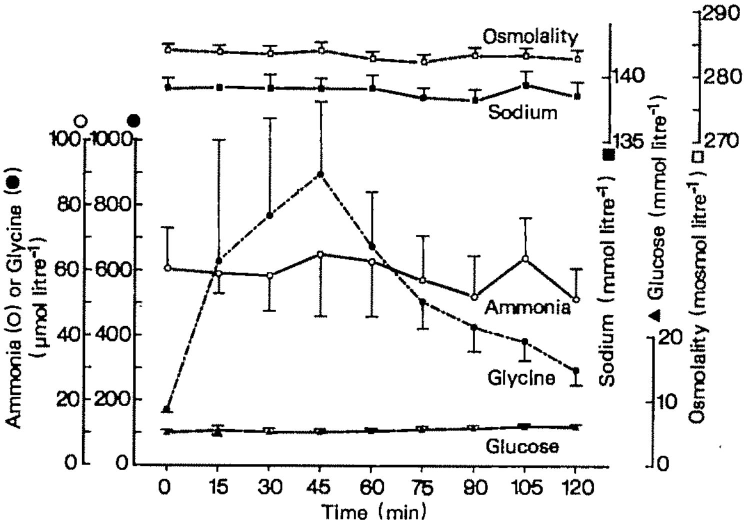

FIG. 5. Mean blood concentrations of glycine (●), ammonia (○), sodium (■) and glucose (▲), and serum osmolality (□) in patients undergoing TURP. Serum glycine concentrations were increased significantly from preoperative values ($P < 0.01$).

and this excludes another possible cause of the increase in latency [11].

Glycine is a non-essential amino acid found abundantly in the body. It readily crosses the blood–brain barrier, where it functions as an inhibitory neurotransmitter in the spinal cord, brain stem and retina [19]. Infusions of glycine have been shown to cause toxicity in man, demonstrated as nausea, vomiting and headache [20]. Glycine is metabolized in the body to ammonia, lactate, pyruvate, alanine and serine. Serum ammonia concentrations were measured because ammonia has been implicated as a cause of neurotoxicity following TURP [13]. Intermediary metabolites known to cause CNS toxicity are glycoxilic acid, which inhibits oxidative phosphorylation, and methylene tetrahydrofolate, which has been implicated in inhibiting the presynaptic uptake of glutamate and other similar endogenous excitants in the central nervous system [21–23]. These metabolites may contribute to CNS toxicity during transurethral prostatectomy.

In summary, we have demonstrated significant prolongation of P_2 latency following TURP and increases in serum glycine concentration during, and following, TURP— although no correlation could be found between these changes. A closer correlation may be found if VEP were measured during the perioperative period at the time of the maximum serum glycine concentration, or VEP changes may be the result of an accumulation of a metabolite of glycine. No significant changes occurred in the serum concentrations of ammonia, glucose or sodium, or in osmolality.

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COMPARISON OF SUFENTANIL–OXYGEN AND FENTANYL–OXYGEN ANAESTHESIA FOR CORONARY ARTERY BYPASS GRAFTING

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S. M. LYONS AND R. S. J. CLARKE

SUMMARY

Haemodynamic variables were compared in 40 adults undergoing coronary artery bypass grafting during anaesthesia induced with either sufentanil 5 $\mu g\ kg^{-1}$ or fentanyl 25 $\mu g\ kg^{-1}$ in combination with pancuronium 0.1 $mg\ kg^{-1}$. Further doses of sufentanil 2.5 $\mu g\ kg^{-1}$ or fentanyl 12.5 $\mu g\ kg^{-1}$ were given before skin incision and again before sternotomy. All patients were receiving β-adrenoceptor blocking therapy. Satisfactory induction of anaesthesia was produced with both drugs and opioid supplementation prevented any marked haemodynamic response to skin incision and to sternotomy. Following induction of anaesthesia, sufentanil produced the greater decrease in mean arterial pressure and left ventricular stroke work index which continued throughout the study. This suggests that, in the doses used in this study, sufentanil is preferable to fentanyl in patients with coronary artery disease.

Sufentanil, a synthetic opioid five to 10 times more potent than fentanyl in humans [1] has been used to produce surgical anaesthesia in patients undergoing coronary artery bypass grafting. A study using 15 $\mu g\ kg^{-1}$ as a single loading dose at induction of anaesthesia reported that this did not totally prevent the hypertensive response relating to sternotomy [2]. In a further study comparing sufentanil and fentanyl for coronary artery surgery, de Lange and colleagues [3] found that a mean dose of sufentanil 4.2 $\mu g\ kg^{-1}$ was required to induce anaesthesia. This study therefore assessed and compared the cardiovascular responses when anaesthesia was induced with sufentanil 5 $\mu g\ kg^{-1}$ and fentanyl 25 $\mu g\ kg^{-1}$ in combination with pancuronium, with further supplementation with opioid before skin incision and before sternotomy.

PATIENTS AND METHODS

With the approval of the local University Medical Ethics Committee, 40 consenting adult patients were studied during coronary artery bypass surgery. All had symptomatic, angiographically proven ischaemic heart disease, with moderate to good left ventricular function (ejection fraction > 40%). Patients with left ventricular aneurysm, valvular disease, or hepatic or renal disorders were excluded from the study.

All patients were controlled on β-adrenergic blocking drugs which were continued until the evening before surgery. Premedication comprised lorazepam 4–6 mg by mouth 2 h before operation and their usual dose of calcium antagonist and nitrate if they were maintained on this therapy. They were allocated by means of a table of random numbers to receive either sufentanil or fentanyl.

ECG monitoring was commenced when the patient arrived in the operating theatre. Peripheral venous, jugular venous and radial artery cannulation was performed under local anaesthesia. A quadruple-lumen thermodilution catheter was floated into the pulmonary artery for measure-

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ment of central venous (CVP), pulmonary artery (PAP) and wedge (PCWP) pressures. Cardiac output was determined using iced injectate (5% dextrose 10 ml), taking the arithmetic mean of three consecutive values within 10% of each other. All cardiac output measurements, pulmonary capillary wedge and central venous pressures were taken at the end of expiration.

Preoxygenation was undertaken for a period of approximately 10 min, during which time baseline measurements of heart rate, systolic, diastolic and mean arterial pressure, central venous, pulmonary artery and pulmonary capillary wedge pressure and cardiac output were recorded. Samples of arterial blood were obtained for gas analysis.

All patients received pancuronium 0.03 mg kg^{-1} 1 min before induction of anaesthesia (table I). The patients received either sufentanil 5 µg kg^{-1} or fentanyl 25 µg kg^{-1} injected over 1 min. All drugs were administered via the central catheter and flushed with 5% dextrose. Time to loss of eyelash reflex was noted, at which time a further dose of pancuronium 0.07 mg kg^{-1} was given. Ventilation was assisted by hand to maintain normocapnia, checked by arterial blood-gas measurements. Cardiovascular measurements were recorded 5 min after the initial dose of pancuronium and intubation was performed at 7 min, with further haemodynamic variables recorded 1 min thereafter. The patient's lungs were ventilated with a 50% air in oxygen mixture using an Engstrom ventilator to maintain normocapnia.

A supplementary dose of sufentanil 2.5 µg kg^{-1} or fentanyl 12.5 µg kg^{-1} was given 1 min before skin incision and also 1 min before sternotomy, haemodynamic variables being recorded before and 1–2 min after both events at time of maximum increase in arterial pressure.

TABLE I. *Time sequence of study*

Time	Event
	Baseline haemodynamics
0	Pancuronium 0.03 mg kg^{-1}
1 min	Sufentanil 5 µg kg^{-1} or fentanyl 25 µg kg^{-1}
Loss of eyelash reflex	Pancuronium 0.07 mg kg^{-1}
5 min	Haemodynamics
7 min	INTUBATION
8 min	Haemodynamics
	Haemodynamics
1 min before skin incision	12.5 µg kg^{-1} fentanyl or 2.5 µg kg^{-1} sufentanil
	SKIN INCISION
1 min after skin incision	Haemodynamics
1 min before sternotomy	12.5 µg kg^{-1} fentanyl or 2.5 µg kg^{-1} sufentanil
	STERNOTOMY
1 min after sternotomy	Haemodynamics

Systemic vascular resistance (SVR), left ventricular stroke work index (LVSWI) and cardiac index (CI) were calculated using a standard computer program.

No fluid was administered during the period of study other than the dextrose used for cardiac output determination. Any muscle rigidity during the study was noted. All patients were questioned the next day on recall of events in the anaesthetic room and during anaesthesia.

The results were analysed using repeated measures analysis of variance, and, where statistically significant effects were observed in the analysis of variance, means were compared by Student's *t* test using the appropriate standard errors derived from the analysis. A significance level of less than 5% was considered significant throughout.

RESULTS

Patients were comparable with respect to age, weight and preoperative drug therapy (table II).

Loss of eyelash reflex occurred in a mean of 67 s (range 45–120 s) and 82 s (range 35–165 s) in the sufentanil and fentanyl groups, respectively, although the difference was not significant.

During the period of manual ventilation before intubation Pa_{CO_2} averaged 5.3 ± 0.55 (SD)kPa in the sufentanil and 5.2 ± 0.75 kPa in the fentanyl group.

Times to skin incision averaged 51 and 46 min and to sternotomy 62 and 58 min in the sufentanil and fentanyl groups, respectively. These

TABLE II. *Demographic data (mean ± SEM)*

	Sufentanil group	Fentanyl group
Number	20	20
Male/female	15/5	13/7
Age (yr)	57 ± 1.5	54 ± 1.5
Weight (kg)	69 ± 2.3	71 ± 2.7
Drugs before op.		
β-Blocker	20	20
Nitrates	14	14
Ca^{2+} blocker	18	18

TABLE III. *Haemodynamic values (mean ± SEM) during study. S = Sufentanil; F = fentanyl. HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; LVSWI = left ventricular stroke work index; SVR = systemic vascular resistance.* *P < *0.05*; **P < *0.01*; ***P < *0.001*

	HR (beat min^{-1})	MAP (mm Hg)	CVP (mm Hg)	MPAP (mm Hg)	PCWP (mm Hg)	CI (litre min^{-1} m^{-2})	LVSWI (g m m^{-2})	SVR (dyn s cm^{-5})
Control								
S	71±2.3	99±2.9	5.3±0.48	15.3±0.77	9.2±0.71	2.7±0.09	46.3±2.14	1613±72.9
F	70±2.6	101±3.3	6.4±0.36	15.4±0.87	10.0±0.81	2.7±1.00	47.9±2.15	1601±81.7
5 min								
S	74±2.9	80±3.5*	6.3±0.53	15.6±0.73	8.3±0.66	2.6±0.09	34.9±2.58	1308±51.9
F	73±2.1	90±3.0	7.9±0.45	15.9±0.84	9.6±0.73	2.7±0.11	40.4±1.73	1432±82.9
After intubation								
S	75±3.1	88±3.1*	6.0±0.48*	15.4±0.79	8.0±0.59	2.6±0.12	38.3±2.55*	1419±60.9
F	75±2.1	98±3.0	8.1±0.64	16.5±0.97	9.8±0.84	2.8±0.12	44.8±2.40	1484±89.5
Before skin incision								
S	68±2.5	81±2.9***	5.7±0.51	14.2±0.72	7.6±0.71	2.3±0.08	33.3±1.76**	1532±79.6
F	73±3.1	96±3.2	7.2±0.60	16.6±0.97	9.6±0.85	2.6±0.16	42.3±2.21	1554±78.8
After skin incision								
S	67±2.4	85±3.4**	6.3±0.51	14.7±0.86	7.9±0.63	2.4±0.07	37.0±1.95*	1515±81.5
F	69±1.8	98±3.2	7.1±0.49	16.6±1.07	10.0±0.73	2.5±0.09	43.8±1.83	1612±79.5
Before sternotomy								
S	69±2.7	93±3.3*	6.0±0.45	15.5±0.87	8.1±0.69	2.5±0.90	41.6±1.91*	1632±97.6
F	71±2.0	102±2.7	7.4±0.57	17.0±1.04	10.5±0.76	2.7±0.11	47.7±2.09	1594±94.6
After sternotomy								
S	72±2.9	94±3.3*	6.4±0.41	15.0±0.84	7.9±0.66	2.4±0.08	39.3±1.83*	1658±91.9
F	73±2.1	104±3.7	7.2±0.53	17.0±0.98	10.3±0.78	2.7±0.11	46.8±2.33	1660±90.5

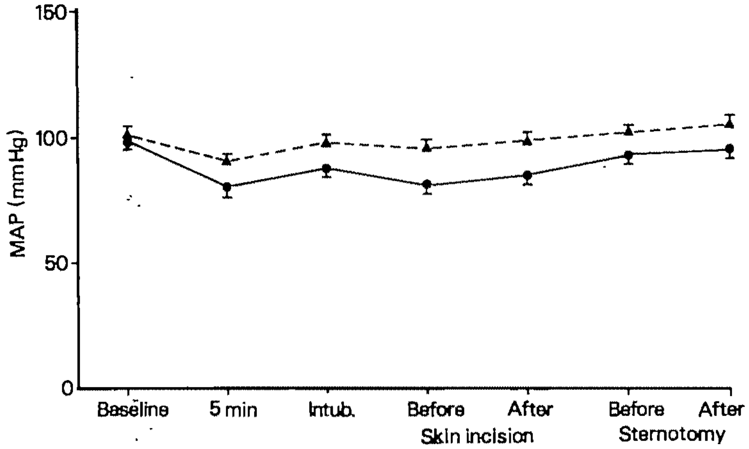

FIG. 1. Mean arterial pressure (±SEM) during the study. ▲——▲ = Fentanyl; ●——● = sufentanil. Intub. = intubation.

differences were not significant. Two patients in the fentanyl and one in the sufentanil group had slight rigidity lasting approximately 30 s. No patient in either group had any recall of events during induction of anaesthesia or the operation.

Haemodynamic values at all the times studied are shown in table III. Analysis of variance showed that the time-course of change in mean arterial pressure was significantly different ($F = 2.49$; $P < 0.05$) in the two groups, with sufentanil producing a greater decrease in pressure following induction which remained lower than with fentanyl throughout the period of study (fig. 1). For CVP and LVSWI the analysis of variance showed a difference in baseline between the groups, therefore analysis was repeated with baseline results used as a covariate in the analysis. The change with time was similar in both groups ($F = 0.42$; $P > 0.05$) but, after adjustment for differences in baseline, LVSWI was significantly smaller following intubation and during the remainder of the study in the sufentanil group ($F = 7.72$; $P < 0.01$). CVP was significantly greater ($P < 0.05$) in the fentanyl group following intubation, but otherwise there was no significant difference between groups during the remainder of the study. Analysis of variance showed no difference between the groups in any of the other haemodynamic indices, although differences with time were noted. Heart rate increased significantly in both groups ($P < 0.05$) following induction and intubation, but returned to baseline values for the duration of the study.

Mean pulmonary and pulmonary capillary wedge pressure showed no significant change during the period of study in either group.

Systemic vascular resistance decreased significantly in both groups ($P < 0.001$) following induction and then increased progressively during the study, with an insignificant increase above baseline following sternotomy.

Cardiac index remained stable during induction and intubation with a decrease from baseline before skin incision ($P < 0.01$).

The mean data shown in table III obscure any particular change in cardiovascular dynamics occurring in individual patients. For this reason cardiovascular data have been reviewed from several individual patients in whom marked changes in mean arterial pressure occurred. One patient who received fentanyl had an increase in mean arterial pressure from a baseline of 106 mm Hg to 131 mm Hg following induction of anaesthesia, associated with an increase in heart rate from 57 to 75 beat min^{-1} and in PCWP from 7 to 11 mm Hg, and a high LVSWI value of 59.1 g m m^{-2}. This high mean arterial pressure was maintained until skin incision with no decrease following further supplementation with fentanyl. Although there was no evidence of myocardial ischaemia as detected on ECG lead CM_5, it was felt necessary to supplement the anaesthetic with halothane after skin incision. This patient was included in the study. One other patient who received fentanyl had a marked increase in mean arterial pressure from 81 mm Hg to 124 mm Hg associated with an increased heart rate from 82 to 117 beat min^{-1}, PCWP 17 mm Hg and LVSWI of 65.2 g m m^{-2} at insertion of skin clips, but this responded to supplementation with fentanyl before skin incision. Both patients reported no recall of events during the operation. One patient in the sufentanil group had a high baseline mean arterial pressure (122 mm Hg) which decreased to 101 mm Hg before skin incision, but increased to baseline values after skin incision and during sternotomy. One sufentanil-treated patient had a mean arterial pressure which decreased from 115 mm Hg at baseline to 70 mm Hg following induction. The lowest mean arterial pressure in the sufentanil treated patients at any time was 62 mm Hg. None of these changes in mean arterial pressure was associated with any evidence of myocardial ischaemia on ECG at any time in either group.

DISCUSSION

In this study induction of anaesthesia was rapid in both groups, explained by the rapid administration of sufentanil and fentanyl over 1 min. Rapid administration of fentanyl produces higher peak blood concentrations and more rapid induction of anaesthesia. It has further been shown that there is little difference in onset of anaesthesia or cardiovascular effects between 15 and 60 $\mu g\, kg^{-1}$ of fentanyl when administered rapidly at 72 $\mu g\, kg^{-1}\, min^{-1}$ [4]. De Lange [3] found that, by increasing the rate of administration of sufentanil to 300 $\mu g\, min^{-1}$, anaesthetic induction was faster; rates above this increased the overall frequency of rigidity without decreasing induction time. The induction time of 1.3 min for sufentanil in De Lange's study is similar to our figure of 62 s, although he found a slower induction time of 4.6 min when fentanyl was administered at 400 $\mu g\, min^{-1}$. In our study fentanyl was administered at approximately 1750 $\mu g\, min^{-1}$, which would explain the more rapid induction time of 82 s.

With such rapid administration of opioid, pretreatment with pancuronium 0.03 mg kg^{-1} 1 min before induction prevented any marked rigidity, and in fact only three patients had slight rigidity lasting 30 s.

This study, therefore, used doses of opioids in the lower therapeutic range administered rapidly to produce induction of anaesthesia and lack of cardiovascular response to intubation. Waller and his colleagues [5], however, found that a single induction dose of fentanyl 60 μg kg^{-1} was insufficient to block haemodynamic changes following sternotomy and Sebel and Bovill [2] found similar inadequacies with a single dose of sufentanil 15 μg kg^{-1}. In our study, therefore, supplements of one-half the original dose of opioid were given before skin incision and before sternotomy in an attempt to ablate the haemodynamic response to surgical stimulus.

Using this opioid regimen, mean arterial pressure was significantly less in the sufentanil group at all times following induction of anaesthesia and during the study, and did not increase above baseline values following sternotomy. The decrease in mean arterial pressure in both groups following induction was initially the result of a decrease in peripheral vascular resistance. In conjunction with this lower mean arterial pressure, the left ventricular stroke work index was also less in the sufentanil group, which is advantageous in patients with ischaemic heart disease.

The transient increase in heart rate in both groups following induction of anaesthesia may be assumed to be an effect of the pancuronium, as this increase was not maintained during the remainder of the study and further supplements of opioids had no effect on the heart rate. Thomson and Putnins [6] found that patients given pancuronium, compared with those given dimethyltubocurarine, had significantly increased heart rates following induction and continuing through to sternotomy, despite the presence of β-adrenergic blockade. However, Pinaud and Souron [7] found that β-adrenergic blockade attenuated the increase in heart rate associated with pancuronium, producing only a slight and transient increase for 5 min after administration of pancuronium, as in our study. Pancuronium increases heart rate by two mechanisms: release of noradrenaline and inhibition of re-uptake of noradrenaline—effects which should be blocked by β-blockade. The second mechanism is by vagal blockade, and since our patients did not receive any vagolytic premedication, this mechanism may be the reason for the increase in heart rate associated with pancuronium in our study.

No difference was found between groups with respect to systemic vascular resistance, unlike the study by Howie and colleagues [8], in which sufentanil produced a greater decrease in SVR than fentanyl when using twice the dose of opioid used in our study. These workers found no difference in mean arterial pressure between groups. However, if the potency ratio is incorrect, the lower doses used in this study may have given a false impression of the effectiveness of sufentanil. If the higher potency ratio of 10 times, rather than five times, had been taken and a larger dose of fentanyl given, there might have been no differences in cardiovascular stability between the groups.

The degree of β-adrenergic blockade present at operation may influence changes in heart rate and arterial pressure during laryngoscopy, skin incision and sternotomy. Stanley, de Lange and Boscoe [9] found that a mean dose of sufentanil 11.4 μg kg^{-1} was required in patients who received long term β-blocking therapy, compared with a mean dose requirement of sufentanil 14.8 μg kg^{-1} in patients not subjected to β-blockade. All patients in this study were receiving β-blocking drugs, although they did not receive any medication on the morning of surgery. This may account for the adequate control of heart rate and arterial pressure obtained with these relatively low doses of sufentanil, although a further study is required to ascertain if this dose of sufentanil is adequate in patients not receiving β-blocking therapy.

In conclusion, all patients in the sufentanil group were adequately anaesthetized. However, two patients in the fentanyl groups had a marked hypertensive response to surgical stimuli, although no awareness was reported, perhaps because of the amnesic properties of the lorazepam premedication. The suggestion that sufentanil was superior to fentanyl in these doses is confirmed by the lower mean arterial pressure and left ventricular stroke work index in the sufentanil group, with no profound hyper- or hypotensive episodes in this group.

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ADRENOCORTICAL HORMONE CONCENTRATIONS IN CHILDREN DURING CARDIOPULMONARY BYPASS WITH AND WITHOUT PULSATILE FLOW

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SUMMARY

Plasma cortisol and ACTH concentrations were measured in two groups of children (aged 1–16 yr). Ten children underwent routine (non-pulsatile) cardiopulmonary bypass and 10 underwent pulsatile bypass under moderate hypothermia (28–32 °C). Comparable increases in cortisol and ACTH concentrations were demonstrated at the onset of bypass and the concentrations of both hormones increased during bypass. In the post-bypass period plasma cortisol concentration increased sharply; there was no further increase in the plasma ACTH concentration. By 24 h the concentrations of both hormones had declined towards baseline values. There were no significant differences between the groups.

The value of pulsatile cardiopulmonary bypass has been investigated widely in adult patients [1–4]. These reports have suggested that pulsatile flow is associated with more physiological organ blood flow and function than non-pulsatile flow. However, an area of continuing controversy concerns the effect of cardiopulmonary bypass (CPB) on adrenocortical function and the response to surgical stress in the adult. For example, Taylor and colleagues [5, 6] reported that non-pulsatile CPB with haemodilution caused a significant decrease in plasma cortisol concentration, possibly secondary to adrenocortical hypofunction, and suggested that adequate cortisol concentrations could be preserved by the addition of pulsatile flow. However, other studies have failed to confirm this finding [7, 8].

Although Williams and co-workers [9] have suggested that pulsatile cardiopulmonary bypass offers some non-specific advantages over non-pulsatile bypass in paediatric practice, adrenocortical function during bypass, and the effect of adding pulsatility, have not been formally assessed in children.

Our study was undertaken to investigate the secretion of cortisol and ACTH in children aged 1–16 yr undergoing cardiopulmonary bypass with and without pulsatile arterial flow.

PATIENTS AND METHODS

Twenty children, admitted for elective cardiac surgery, were selected for study and allocated randomly to two comparable groups. Ten children underwent non-pulsatile cardiopulmonary bypass (group I) and 10 underwent pulsatile bypass (group II). Data for both groups are detailed in table I. The lower limit of age was 1 yr, since the circadian rhythm of the adrenal secretion of cortisol is not clearly developed before that age [10]; the upper age limit was 16 yr. Patients with complex cyanotic abnormalities were excluded, since the high haematocrit values obtained frequently in such patients precluded small volume sampling for plasma hormone assay. The study was approved by the hospital Ethical Committee. Two surgeons participated.

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TABLE I. *Details of patients undergoing pulsatile and non-pulsatile cardiopulmonary bypass. ASD = Atrial septal defect; VSD = ventricular septal defect; a–v = atrio–ventricular; PAPVD = partial anomalous pulmonary venous drainage. Patch = right ventricular outflow tract patch*

	Age (yr)	Weight (kg)	Surface area (m^2)	Operative procedure
Group I: Non-pulsatile	1.0	9	0.33	Closure VSD
(n = 10) (5M/5F)	1.5	11	0.50	Closure ASD
	1.9	8	0.40	Closure a–v canal
	5.1	15	0.66	Closure ASD
	7.0	18	0.70	Closure VSD
	7.6	23	0.90	Closure VSD
	8.5	29	1.00	Aortic valvotomy
	11.9	44	1.30	Aortic valvotomy
	12.9	39	1.31	Closure ASD
	15.8	33	1.20	Closure ASD
Group II: Pulsatile	1.0	8	0.42	PAPVD
(n = 10) (3M/7F)	1.2	10	0.46	Closure ASD
	2.5	11	0.50	Closure ASD
	3.7	12	0.58	Closure ASD
	5.6	16	0.67	Closure ASD
	6.7	37	1.26	Closure ASD
	10.1	35	1.19	Closure ASD
	10.5	27	0.98	Closure VSD
	11.0	27.5	0.94	Patch
	15.9	47	1.40	Aortic valvotomy

Premedication consisted of diazepam and droperidol each 0.2 mg kg^{-1} given by mouth 2 h before the induction of anaesthesia with sodium thiopentone 5 mg kg^{-1} i.v. Neuromuscular blockade was obtained by the administration of either tubocurarine 0.5 mg kg^{-1} or pancuronium 0.1 mg kg^{-1}, and anaesthesia was maintained with nitrous oxide in oxygen supplemented with increments of papaveretum i.v., and 0.5% halothane if necessary. Standard perioperative monitoring consisted of ECG, intra-arterial pressure, CVP and urinary output.

Venous blood was sampled to allow measurement of ACTH and cortisol concentrations at the following times:

(1) Before operation—2 days before surgery between 10.00 a.m. and 11.00 a.m.

(2) After the induction of anaesthesia but before skin incision.

(3) 2 min after starting bypass (CPB I).

(4) 2 min before the end of bypass (CPB II).

(5) 2 h after arriving in the I.T.U.

(6) 24 h after operation.

Heparinized blood was centrifuged within 15 min of withdrawal and the plasma decanted and frozen in liquid nitrogen. Thereafter, samples were stored at −20 °C until required for analysis. Serum cortisol concentration was measured by radioimmunoassay (RIA) using the Amerlex kit (Amersham International) which uses a highly specific anti-cortisol serum which is coupled to solid phase and a ^{125}I-cortisol derivative tracer. The method performed with mean intra- and inter-assay coefficients of variation of 6.0% and 9.2%, respectively.

Plasma ACTH concentration was measured using a double antibody RIA which uses M.R.C. 74/555 as standard ACTH, highly purified human ACTH supplied by P. J. Lowry, St Bartholomew's Hospital, London for radioiodination and an antibody purchased from the IgG Corporation Nashville, Tennessee U.S.A. The ACTH assay has a sensitivity of 5 ng $litre^{-1}$ for unextracted plasma and interassay co-efficients of variation of 15% within the 0.8–0.9 normal range (< 80 ng $litre^{-1}$).

Pulsatile flow was produced by a standard ECG-triggered Stockert roller pump system [11], which is a modified roller pump generating a pulsatile flow pattern by rapid acceleration and a deceleration of the pump head. Pulsatility was obtained through 75% of the cardiac cycle and a forward flow was maintained throughout. The pump was timed from the ECG and during the asystolic cross-clamp period the child was pulsed at the same rate as was present immediately before

TABLE II. *Details of CPB in pulsatile and non-pulsatile groups of patients. No significant differences between groups*

	Pulsatile	Non-pulsatile
MAP during CPB (mm Hg)	42	37
Mean pH at end of CPB	7.31	7.3
Mean duration of CPB (min)	54	60
Mean cross-clamp time (min)	30	36

the application of the cross-clamp and the infusion of the cardioplegia solution.

Throughout the system the size of the tubing was 100 mm, with aortic cannulae ranging from 4.7 to 5.0 mm internal diameter, depending on the size of the child. A flow rate of 2.4 litre m^{-2} min was used in both pulsatile and non-pulsatile groups. A bubble oxygenerator was used: a Shiley S70 in small children and an Optiflo II in older patients.

The pump circuit was primed with lactated Ringer's solution and concentrated red cells were added to achieve a packed cell volume of 25% on bypass. Children were cooled to moderate hypothermia (28–32 °C) and rewarmed to a temperature of at least 35 °C before being weaned from bypass.

During the period of cross-clamping, St Thomas's cardioplegic solution 25 ml kg^{-1} was infused and topical hypothermia was used by bathing the heart in cold physiological saline solution.

Correction for the effect of haemodilution on plasma hormone concentration was obtained by using the formula:

$$\text{Corrected concentration} = \text{Plasma hormone concn} \times \frac{\text{Pre-op. PCV}}{\text{PCV at time of sample}}$$

Artificial ventilation was continued in the postoperative period until the child was stable haemodynamically, and until there was minimal drainage via the chest drain. Sedation was achieved with i.v. morphine 0.1 mg kg^{-1} or diazepam 0.2 mg kg^{-1} at 1-h intervals as necessary.

Intergroup data were analysed using Student's unpaired t test.

RESULTS

Mean arterial pressure (radial artery) during bypass, mean pH at the end of bypass, mean durations of bypass, and of cross clamping, for both groups are shown in table II. They were comparable, with no significant differences. Mean doses of papaveretum for the duration of anaesthesia were 0.66 mg kg^{-1} in the non-pulsatile and 0.72 mg kg^{-1} in the pulsatile group (ns). These doses were well below the equivalent morphine doses which suppress cortisol during CPB [12]. Hormone data corrected for haemodilution for both groups throughout the period of study are shown in tables III and IV.

Plasma cortisol and ACTH concentrations increased significantly, and to the same extent, in both groups during surgery and there was no decrease in the concentration of either hormone during bypass. After the return to the natural circulation, there was an immediate increase in plasma cortisol concentration, followed by a decrease towards basal values at 24 h. Plasma ACTH concentration did not increase further in the post-bypass period and values had returned to normal by 24 h after surgery.

DISCUSSION

This study has confirmed that, in children, concentrations of adrenocortical hormones (and by implication adrenocortical function) are not significantly affected by routine non-pulsatile bypass. Furthermore, the addition of pulsatile

TABLE III. *Mean ± SD plasma cortisol concentrations (haemodilution corrected) (nmol litre^{-1})*

	Group I Non-pulsatile ($n = 10$)	Group II Pulsatile ($n = 10$)	t	P
Before op.	423.0 ± 51.2	352.0 ± 62.93	0.876	ns
Before incision	426.0 ± 73.7	521.8 ± 105.94	−0.741	ns
CPB I	703.9 ± 61.03	831.1 ± 71.47	−1.355	ns
CPB II	848.9 ± 85.38	1012.3 ± 92.02	−1.303	ns
2 h after op.	1200.7 ± 106.88	1156.3 ± 209.34	0.189	ns
24 h after op.	784.6 ± 66.4	741.1 ± 77.79	0.425	ns.

TABLE IV. *Mean ± SD plasma ACTH concentrations (haemodilution corrected) (ng litre^{-1})*

	Group I Non-pulsatile ($n = 10$)	Group II Pulsatile ($n = 10$)	t	P
Before op.	36.0 ± 5.09	44.4 ± 13.06	0.599	ns
Before incision	56.2 ± 18.47	71.0 ± 35.1	0.374	ns
CPB I	198.5 ± 59.45	182.0 ± 29.91	−0.248	ns
CPB II	255.4 ± 63.56	236.0 ± 47.75	−0.244	ns
2 h after op.	227.7 ± 59.45	208.7 ± 47.75	−0.249	ns
24 h after op.	32.7 ± 10.34	16.4 ± 5.19	−1.782	ns

flow produced no alteration in the pattern of secretion of either hormone. However, these findings have to be considered within the confines of the anaesthetic and bypass techniques used. Our findings concur to some extent with those of Frater and colleagues [7], who performed a comparative study of patients undergoing coronary artery bypass grafting (with haemodilution and hypothermia) using pulsatile and non-pulsatile flow. They were unable to demonstrate any difference between the concentrations of plasma cortisol at the beginning and at the end of bypass, and no difference between the pulsatile and non-pulsatile groups. Kono and co-workers [8] measured plasma cortisol and ACTH concentrations during pulsatile and non-pulsatile bypass and were unable to demonstrate any increase in cortisol concentration, although there was a slight increase in ACTH concentration. However, there was no change in the concentration of either hormone on the institution of pulsatile flow.

Many differences exist between these studies and those of Taylor and colleagues [11, 13] and, as a result, few direct comparisons can be made. Different sampling times were used. Moderate hypothermia was used by Frater and colleagues [7] and by Kono and co-workers [8]: Taylor and colleagues [11, 13] used normothermia. Frater and colleagues [7] and Kono and co-workers [8] used pulsatile assist devices, which produce pulsatility without markedly increasing the flow; Taylor and colleagues [11] used a Stockert roller pump which produces pulsatile perfusion only during the period of absent left ventricular ejection—pulsatility being produced as a result of pulsatile flow. Other important differences can be found in the anaesthetic techniques used by the three groups. Frater and associates [7] electively used β-blockade up to the commencement of anaesthesia, and in the postoperative period. Morphine 150 μg kg^{-1} was given as premedication and enflurane was administered as required during bypass by the perfusion team. Kono and co-workers [8] gave few details of the anaesthetic used, but it has to be noted that the absence of any intraoperative cortisol response suggests that a technique which suppressed the "stress response" could have been used.

The inherent differences between children and adults make any direct comparisons between our study and previous ones difficult, but the design of the present study most closely resembles that of Taylor and colleagues [11]. The Stockert roller pump was used to produce pulsatility, and the same flow rate (2.4 litre m^{-2} min) was used. Anaesthesia consisted of nitrous oxide in oxygen and incremental papaveretum ± 0.5 % halothane with no inhalation agent being used during bypass. β-Blockade was not used. The sampling times were similar except for the second, which we obtained between the induction of anaesthesia and the skin incision, instead of immediately before the onset of bypass. The priming fluid differed from the adult series and the children had lower mean arterial pressures, although this would not reflect central arterial pressures since, in children, a wide central–peripheral arterial pressure gradient develops, especially when hypothermia is used. Although we now follow the common practice in children of vasodilatation before and after bypass, such a technique was not used in the present study.

The common factor of moderate hypothermia used by Frater and colleagues, Kono and co-workers and ourselves deserves comment. It may be that this modified the stress response or that the associated changes in systemic vascular resistance have an effect on the quality of pulsatility. Certainly, the differences in hormone secretion bear little relationship to the flow rates used by the four groups. Frater and colleagues used 3 litre m^{-2} min, Kono and co-workers 2.25 litre m^{-2} min and Taylor and colleagues and ourselves 2.4 litre m^{-2} min. These were associated with a plateau of cortisol concentration during bypass in Frater's study, a decrease during bypass in Kono's study and an increase between CPB I and CPB II in both pulsatile and non-pulsatile groups in our study. In the study by Taylor and colleagues [11] there was a significant increase in concentration between CPB I and CPB II in the pulsatile group.

The only comparative study in children was carried out by Williams and associates [9], who compared pulsatile perfusion with non-pulsatile perfusion for rapid core cooling and re-warming of infants during circulatory arrest. They suggested that pulsatile bypass was superior, with more uniform cooling and re-warming, shorter perfusion time, improved urine production, less metabolic acidosis and reduced postoperative ventilation time. The conclusion drawn was that pulsatile perfusion was more physiological, although there was criticism that this conclusion was based on somewhat subjective and imprecise indices. It has to be noted that, once again, differences in anaesthesia and perfusion make comparisons difficult. A pulsatile assist device was used to produce pulsatility and the patients were in receipt of α-adrenoceptor blockade to produce maximum vasodilatation.

Our study may be criticised on the grounds that we have not quantified the pulsatile flow used. In a review of pulsatile and non-pulsatile cardiopulmonary bypass, Hickey, Bucklin and Philbin [14] recognized the difficulty of comparing studies in the absence of any method for quantification or standard definition of the various types of pulsatile flow used. They postulated that an explanation for the inconsistent results from studies of cardiopulmonary bypass lay in the fact that different forms of pulsatile perfusion were being investigated, only some of which were effective, and suggested that further studies should aim to define what, in fact, constitutes effective pulsatile flow.

Grossi and co-workers [15] carried out a study in dogs undergoing normothermic pulsatile bypass using continuous spectral analysis of flow signals combined with pulse rate to quantify the pulsatility of blood flow, and noted changes in serum lactate concentration as an indication of end-organ flow. Their method allowed comparison of different pulsatile waveforms and provided a means of identification of optimal pulsatile flow. We await reports of similar studies in patients.

In conclusion, the place of pulsatile cardiopulmonary bypass is still not clearly defined, particularly with respect to children. Our data suggest that *under the conditions of this study* there is no evidence of adrenocortical hypofunction during non-pulsatile bypass and that children can respond to various intraoperative stresses by increasing the secretion of cortisol and ACTH.

It may be that a closely controlled study of other indices will confer some advantage of pulsatile over non-pulsatile flow, but within the limits of the pituitary–adrenal axis no such advantage appears to exist.

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DOUBLE-BLIND COMPARISON OF THE EFFICACY AND SAFETY OF SINGLE DOSES OF MEPTAZINOL AS A SUPPOSITORY AND MORPHINE BY I.M. INJECTION

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SUMMARY

The analgesic efficacy of a 150-mg meptazinol suppository was compared with that of morphine 10 mg i.m. in the treatment of moderate postoperative pain. Two groups of 15 female patients took part in a 4-h, randomized double-blind, double-dummy study on the first day after elective abdominal hysterectomy. Meptazinol did not provide satisfactory analgesia in five patients ($P < 0.05$). *A decrease in mean pain scores (linear analogue scale and verbal rating scale) was seen after the administration of meptazinol, but this was not as great as that produced by morphine i.m., nor was it as long in duration. Significant changes in arterial pressure, heart rate and ventilatory rates were not seen in association with the administration of meptazinol, but were observed after the administration of morphine.*

The parenteral administration of meptazinol, a centrally-acting analgesic with mixed agonist–antagonist properties [1], has been shown to be effective in the management of postoperative pain when compared with papaveretum, pethidine and pentazocine [2,3]. The rectal administration of meptazinol to animals and man has been shown to result in rapid absorption with peak plasma concentrations occurring 30 min after administration [4]. Plasma concentrations achieved by this route were within the therapeutic range [5]. The efficacy of meptazinol administered per rectum for the management of postoperative pain has not been determined.

A double-blind, double-dummy study was designed to assess the efficacy of meptazinol suppositories in comparison with a conventional dose of morphine i.m. in the management of moderate or severe postoperative pain.

PATIENTS AND METHODS

Female patients (ASA status I or II) were studied over a 4-h period on the first day after elective abdominal hysterectomy. The study was approved by the District Ethics committee and informed consent obtained from each subject at the preoperative visit. Anaesthesia for the operative procedure was standardized and all analgesia from the time of operation to inclusion in the study was given as papaveretum 20 mg i.m.

Patients were admitted to the trial when they complained of pain described as moderate, severe or intolerable on a five-point verbal rating scale (VRS) (1 = no pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain; 5 = intolerable pain). Patients not complaining of this degree of pain, those who were more than 20% above their ideal body weight, those who had received analgesic or sedative medications within the preceding 3 h and those who gave a history of sensitivity to opioids were excluded from the trial.

Patients were allocated randomly to one of two treatment groups. The meptazinol group received meptazinol 150 mg by suppository and 0.9% sodium chloride 1 ml i.m. into the upper outer quadrant of the buttock. The morphine group received a placebo suppository and morphine

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sulphate 10 mg as a 1-ml i.m. injection. All treatments were administered by a single trained nurse observer. Active and placebo suppositories were identical in appearance and were prepared as 2-g suppositories with Witepsol H 12/Span 20 excipients. All ampoules were identical in appearance.

Assessments were made by the same nurse observer before the administration of the analgesic–placebo combination and at 30, 60, 120, 180 and 240 min thereafter. Pain was assessed using the five-point VRS and a 10-cm linear analogue scale (LAS). Sedation, nausea and dizziness were also assessed by LAS. Episodes of vomiting and any requirement for anti-emetic drugs were documented.

Arterial pressure and heart rate were measured at each time point using a semi-automated sphygmomanometer (Copal H.A. 21); ventilatory rate was counted by the nurse observer. Sleeping patients were not roused and were excluded from the analysis at that time point, but were assumed to have adequate analgesia.

Any patient failing to achieve adequate analgesia at any point was withdrawn from the study and given additional analgesia (morphine 10 mg i.m.). Data from these patients was included up to the time of their withdrawal from the trial.

Statistical analysis of the results used Student's *t* test for data with a normal distribution, Wilcoxon rank sum test for data derived from LAS and VRS and Fisher's exact test, as appropriate.

TABLE I. *Demographic data (mean, SEM)*

	Meptazinol group	Morphine group
Age (yr)	40.46 (1.54)	40.0 (1.23)
Height (cm)	161 (1.95)	163 (1.64)
Weight (kg)	63.26 (1.81)	57.0 (2.81)

RESULTS

Thirty patients entered the trial. Demographic data are given in table I and show that the patients were evenly matched for age, height and weight. The groups were comparable as regards the time from operation to entry to the study, the time from the last administration of analgesic before entry to the study and the quantity of analgesic agent administered since the operation.

The 15 patients who received morphine all completed the 4-h study period, but five of the 15 patients who received meptazinol were withdrawn because of inadequate analgesia ($P < 0.05$). These patients were withdrawn between 145 min and 195 min after the administration of the analgesic–placebo combination.

The meptazinol group showed a significant decrease in mean LAS for pain at 30 and 120 min compared with pre-treatment values ($P < 0.05$) (table II). In the morphine group mean LAS for pain was decreased from pre-treatment values at all assessment points ($P < 0.01$). The morphine group showed significantly lower mean LAS for pain at the 30- and 60-min assessments when

TABLE II. *Mean (±SEM) linear analogue scores for pain, sedation, nausea and dizziness.* n = *Number of patients included at each assessment. Difference from meptazinol group:* *$P < 0.05$; **$P < 0.01$. *Difference from baseline values:* $P < 0.05$; $P < 0.01$

Time (min)	*n*	Pain	Sedation	Nausea	Dizziness
Meptazinol group					
0	15	5.7 (0.39)	6.8 (0.62)	3.0 (0.68)	3.5 (0.94)
30	15	3.4 (0.55)††	6.5 (0.77)	2.6 (0.77)	2.7 (0.73)
60	14	3.6 (0.72)	6.6 (0.68)	2.3 (0.62)	3.2 (0.76)
120	15	3.5 (0.63)†	6.6 (0.71)	2.9 (0.62)	3.2 (0.75)
180	10	4.4 (1.03)	7.1 (0.84)	2.7 (0.81)	2.3 (0.76)
240	10	4.9 (0.88)	5.6 (0.82)	2.8 (0.78)	1.7 (0.79)
Morphine group					
0	15	5.8 (0.50)	4.7 (0.73)*	1.4 (0.68)*	2.1 (0.80)*
30	15	1.7 (0.39)*††	5.6 (0.86)	0.7 (0.43)	0.5 (0.18)
60	14	1.1 (0.33)*††	4.8 (0.94)	0.9 (0.44)	0.5 (0.18)
120	14	1.9 (0.55)††	4.1 (0.87)	1.0 (0.64)	0.6 (0.21)
180	13	2.2 (0.35)††	2.8 (0.81)	0.6 (0.34)	0.6 (0.25)
240	15	3.2 (0.43)††	2.9 (0.90)	1.3 (0.68)	0.6 (0.22)

TABLE III. *Pain scores derived from verbal rating scales (mean ± SEM). Difference from meptazinol group:* *P < *0.05;* **P < *0.01. Difference from baseline values:* †P < *0.05;* ††P < *0.01*

Time (min)	Meptazinol group	Morphine group
0	3.2 (0.1)	3.2 (0.11)
30	2.2 (0.1)††	1.9 (0.15)††
60	2.4 (0.17)††	1.7 (0.18)*††
120	2.5 (0.21)†	1.9 (0.16)**††
180	2.5 (0.37)	2.0 (0.13)††
240	2.8 (0.31)	2.6 (0.16)††

compared with the meptazinol group ($P < 0.05$) (table II).

There were significant differences between the groups for pain scores as assessed by VRS (table III). The meptazinol group showed lower mean VRS at 30, 60 and 120 min compared with pre-treatment values ($P < 0.05$). The mean VRS in the morphine group was significantly decreased throughout compared with pre-treatment values ($P < 0.01$). The morphine group showed lower mean VRS scores at 60 and 120 min compared with the meptazinol group at these times ($P < 0.05$).

The pre-treatment mean LAS for nausea, sedation and dizziness (table II) were significantly lower in the morphine group than in the meptazinol group ($P < 0.05$). There was no significant deviation from control values in either group. Three patients in the meptazinol group had episodes of vomiting necessitating treatment with an anti-emetic; no patients in the morphine group suffered these sequelae. This difference did not achieve statistical significance.

The patients receiving meptazinol displayed no change in arterial pressure, heart rate or ventilatory rate—except that there was a significant increase in the mean heart rate at 240 min compared with control values ($P < 0.05$) (table IV). In the morphine group there was a small but significant decrease in mean systolic and diastolic arterial pressures. Mean systolic arterial pressures were significantly decreased at 30, 60 and 120 min relative both to the pre-treatment value and to arterial pressure in the meptazinol group at the same time points ($P < 0.05$). At 180 min mean systolic arterial pressure was significantly decreased from the control value ($P < 0.05$). The mean diastolic arterial pressure in the morphine group was significantly decreased compared with the pre-treatment value at all time points and was significantly decreased compared with the meptazinol group at 30, 60 and 120 min ($P < 0.05$). The mean heart rate in the morphine group was significantly decreased at 30 min compared with control values ($P < 0.05$), but did not differ significantly from heart rate in the meptazinol group. The mean ventilatory rate in the morphine group was significantly decreased at 30 and 60 min compared with control values ($P < 0.01$), but did not differ significantly from that in the meptazinol group.

The mean time to next administration of analgesic agent was 5.03 h (range 2.25–16.5 h) in the meptazinol group and 5.8 h (range 4–12.5 h)

TABLE IV. *Arterial pressures, heart and ventilatory rates (mean ± SEM). Difference from meptazinol group:* *P < *0.05;* **P < *0.01. Differences from baseline values:* †P < *0.05;* ††P < *0.01*

Time (min)	Systolic AP (mm Hg)	Diastolic AP (mm Hg)	Heart rate (beat min^{-1})	Ventilatory rate (b.p.m.)
Meptazinol group				
0	125.1 (1.9)	79.6 (2.01)	80.6 (11.6)	14.6 (0.7)
30	127.4 (2.4)	79.1 (2.6)	82.6 (3.0)	14.0 (0.5)
60	131.1 (3.4)	81.9 (1.9)	81.7 (2.6)	14.8 (0.7)
120	128.7 (2.9)	80.9 (2.1)	86.8 (2.9)	14.5 (0.6)
180	123.7 (4.1)	78.4 (1.7)	86.3 (3.2)	14.5 (0.6)
240	129.4 (3.4)	76.4 (1.7)	88.1 (3.3)†	15.1 (0.6)
Morphine group				
0	130.6 (2.8)	81.5 (1.6)	82.8 (3.8)	15.2 (0.5)
30	118.8 (3.2)*††	71.4 (2.5)*††	78.6 (3.4)†	13.4 (0.4)††
60	120.1 (3.9)*††	73.6 (2.3)*††	83.4 (3.9)	13.4 (0.4)††
120	119.6 (3.3)*†	71.3 (1.2)**††	81.5 (4.4)	14.5 (0.6)
180	122.7 (4.3)†	75.4 (2.4)†	81.0 (3.8)	14.0 (0.5)
240	123.5 (3.5)	74.6 (2.2)†	83.1 (3.9)	14.2 (0.5)

in the morphine group. This difference was significant ($P < 0.05$).

DISCUSSION

This study suggests that meptazinol 150 mg administered by the rectal route does not produce relief of moderate pain which is as good, in terms of either quality or duration, as that produced by i.m. morphine in conventional dosage. A decrease in pain scores (LAS and VRS) was seen in the meptazinol group, but these returned towards control values after the 120-min assessment. In contrast, the administration of morphine i.m. produced effective and prolonged pain relief.

The exclusion of the withdrawn patients from further statistical analysis had the effect of selecting the patients in whom meptazinol provided adequate analgesia and may thus bias the study. However, this may be offset by the inclusion, up to the 120-min assessment, of patients who were to be withdrawn subsequently from the study because their pain was becoming intolerable. The alternative to this approach would be to exclude entirely those patients who were withdrawn from the trial. Again, this would bias the results in favour of meptazinol. However, analysis on this basis yields results which do not differ materially from those reported above and thus does not affect the principal conclusion of the study: namely, that meptazinol did not provide adequate analgesia in one-third of the study group.

The difference in pre-treatment scores for nausea, sedation and dizziness between the groups does not appear to be related to any identifiable factor such as anaesthesia or prior analgesic administration and must be assumed as being attributable to chance. No direct comparison between the groups is, therefore, possible with respect to these factors.

The use of meptazinol by parenteral administration as an analgesic agent after abdominal hysterectomy has been studied in the immediate postoperative period [2,3] and on the first day after operation [6]. In these studies, meptazinol compared favourably with pethidine, papaveretum and pentazocine in terms of both analgesic efficacy and duration of analgesic effect. Meptazinol has also been shown to be superior to placebo when administered by mouth to postoperative patients [7]. The conclusions of the present study are not in agreement with these results. Two explanations are apparent for this discrepancy: either adequate plasma concentrations of meptazinol were not achieved or the drug was inadequate as an analgesic under the circumstances of this study.

Pharmacokinetic evaluation of rectally administered meptazinol showed that absorption was rapid, although somewhat variable. Peak plasma concentrations of 39–190 ng ml^{-1} have been reported within 30 min of insertion of a suppository containing meptazinol 75 mg [8] and concentrations in excess of 100 ng ml^{-1} have been reported after rectal administration of meptazinol 100 mg [9]. These plasma concentrations are within the proposed therapeutic range of 25–250 ng ml^{-1} [5]. Plasma concentrations after rectal administration were similar to concentrations observed after i.m. administration of the same dose [9]. Absorption would seem to be substantial as 65–90% of the administered dose was recovered from the urine [4]. Elimination of meptazinol from the plasma occurs in a monoexponential manner after rectal administration, with a half-life of approximately 2 h [4] and thus shows a pattern of elimination similar to that seen after parenteral administration [8]. A pharmacodynamic study has suggested that, after i.v. injection, a peak analgesic effect is seen within 5 min, but that the duration of the analgesia is approximately 2–3 h [10]—a finding confirmed by the present study.

The dose of meptazinol administered in this study, 150 mg, is the maximum recommended by the manufacturers in the data sheet and would be expected to produce plasma concentrations within the range associated with analgesia. No factors were present that might have impaired rectal absorption. It is possible that the previously administered opioid agonist analgesics could have interacted with the partial agonist meptazinol to decrease its effectiveness. However, the plasma concentrations of morphine likely to have been present at the commencement of the study would have been small and no such interaction has been reported in respect of analgesia.

Meptazinol may have some advantages as a postoperative analgesic. It is not a controlled drug and, therefore, is not subject to stringent administration procedures. The potential for severe side effects such as respiratory or cardiovascular depression seems to be low [2,11]; no evidence of either was seen in this study. However, it has been suggested that the administration of meptazinol may be associated with a high incidence of nausea and vomiting after administration to patients [12] and to healthy volunteers [11]. This has not been confirmed in other studies, which showed no greater incidence of nausea after meptazinol than after equipotent doses of pethidine or pentazocine [2, 6]. There is no evidence of an increased incidence of nausea compared with morphine from the present study. The rectal route of administration may also be advantageous; patients are spared repeated i.m. injections and no specialized equipment or procedures are required.

We conclude that meptazinol, administered by the rectal route, has some efficacy in the management of moderate postoperative pain, but the relief of pain achieved was not as good as that achieved by morphine i.m. in conventional dosage.

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EFFECT OF NICARDIPINE HYDROCHLORIDE ON REGIONAL HYPOXIC PULMONARY VASOCONSTRICTION

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The mechanism of hypoxic pulmonary vasoconstriction (HPV) has not been elucidated fully, but has been attributed to the direct effect of hypoxia on pulmonary vascular smooth muscle or release of vasoactive mediators. It has been shown that the response is probably associated with small diameter pulmonary arteries [1, 2]. A recent study reported that hypoxia-induced Ca^{2+}-dependent action potentials were observed in small pulmonary arteries *in vitro* [3]. If it is postulated that HPV is induced by a direct action of hypoxia on smooth muscle cells and initiated by transmembrane Ca^{2+} influx, then calcium channel blockers should abolish or attenuate the response.

Nicardipine hydrochloride is a calcium channel blocker with marked vasodilator properties. It acts on cell membranes of vascular smooth muscle to inhibit voltage-dependent calcium influx [4]. Although nicardipine has been used widely in clinical practice, its effect on HPV has not been investigated. This study was designed to examine the effects of nicardipine on regional hypoxic pulmonary vasoconstriction and to clarify if the response results from a direct action on pulmonary vessels.

SUMMARY

The effects of nicardipine hydrochloride on regional hypoxic pulmonary vasoconstriction (HPV) were investigated in 14 open-chest mongrel dogs. In a second group of seven dogs, HPV responses with nicardipine were assessed during constant cardiac output controlled by inflation of a balloon placed in the inferior vena cava, as higher doses of nicardipine significantly increased cardiac output. In the group with uncontrolled cardiac output, selective ventilation of the left lower lobe lung (LLL) with 100% nitrogen caused a significant decrease in blood flow to the lobe ($\dot{Q}_{LLL}/\dot{Q}_t$) to 47.8 ± 5.5% and an increase in vascular resistance of the LLL (PVR_{LLL}) from 6018 ± 884 to 13807 ± 1162 dyn s cm^{-5}. Testing hypoxic responses during infusion of nicardipine 1, 3 and 6 $\mu g\ kg^{-1}\ min^{-1}$ showed a dose-dependent depression of HPV response. Infusions of nicardipine 3 and 6 $\mu g\ kg^{-1}\ min^{-1}$ with LLL hypoxia resulted in a slight decrease in lobar blood flow, and a hypoxia-induced increase in PVR_{LLL} was not statistically significant. In the controlled cardiac output group, attenuation of HPV responses by nicardipine was similar to that in the uncontrolled cardiac output group.

MATERIALS AND METHODS

Fourteen healthy mongrel dogs of both sexes (weight range 10–13 kg) were anaesthetized with secobarbitone 10 mg kg^{-1} i.v. and neuromuscular block induced with pancuronium 0.4 mg kg^{-1}. The lungs were ventilated via a tracheal tube by a volume-preset ventilator (KN-50, Natsume). Additional doses of secobarbitone 5 mg kg^{-1} i.v. and pancuronium 0.2 mg kg^{-1} i.m. were given as required. A balloon-tipped double-lumen catheter was positioned in the pulmonary artery via the left external jugular vein for measurement of pulmonary artery pressure (PAP) and sampling of mixed venous blood. A catheter was placed in the femoral artery for measurement of systemic arterial pressure (AP) and sampling of arterial blood. A polyethylene catheter was placed in the vena cava via the right femoral vein for measurement of central venous pressure (CVP). Lactated Ringer's solution was administered i.v. at a rate of 10 ml kg^{-1} h^{-1} throughout the study. Following thoracotomy through the left 4th–5th intercostal space, a catheter was inserted directly to the left

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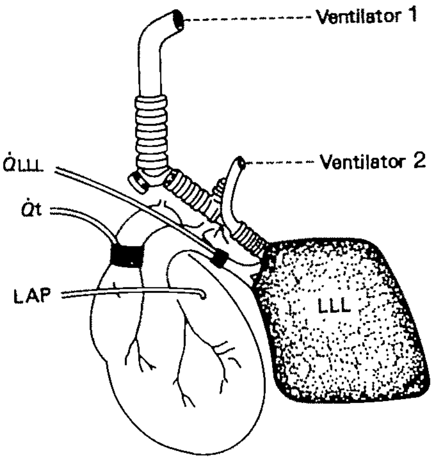

FIG. 1. Schematic diagram of the experimental preparation. The blood flow to the left lower lobe ($\dot{Q}$LLL) and cardiac output ($\dot{Q}$t) were monitored by electromagnetic flow probes. Two ventilators provided independent ventilation.

atrium. AP, PAP, CVP and left atrial pressure (LAP) were recorded simultaneously using a polygraph 142-8 (San-ei Instrument Co.). Electromagnetic flow probes (MFV 1100, Nihon Kohden) were attached around the ascending aorta and left lower lobe (LLL) pulmonary artery after minimal dissection for measurement of cardiac output ($\dot{Q}$t) and LLL pulmonary blood flow ($\dot{Q}$LLL). The flow probes were calibrated with known blood flows through excised vessels using a thermodilution technique. The LLL bronchus was incised and intubated distal to a ligature and ventilated independently with a small-animal ventilator (R-50, Aika) (fig. 1). Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration and airway pressure equal to values for the remaining lung. Arterial $P\text{CO}_2$ was maintained at approximately 4.8 kPa by adjusting the rate of ventilation. Metabolic acidosis was corrected as necessary by infusion of 7% sodium bicarbonate to maintain pH at 7.40. The expiratory tubes of both ventilators were immersed in water to maintain a positive end-expiratory pressure (PEEP) of 3 cm H_2O. Hypoxia of the LLL was induced by alternating the ventilating gases from 100% oxygen (LLL normoxia) to 100% nitrogen for 10-min periods (LLL hypoxia). This period was chosen as a previous study had demonstrated maximum hypoxic responses within 10 min [5]. The remainder of the lung was ventilated constantly with 30–40% oxygen to obtain a Pa_{O_2} of approximately 24 kPa during the period of LLL normoxia. Inspired oxygen concentration ($F\text{I}_{O_2}$) was monitored with an oxygen analyser (OMD 100, Aika).

Responses to hypoxia were calculated as the percentage reduction in the fraction of cardiac output perfusing the LLL ($\dot{Q}$LLL/$\dot{Q}$t) from the LLL normoxic value and as an increase in pulmonary vascular resistance of the LLL (PVRLLL). PVRLLL was calculated from the blood flow to LLL and the perfusion pressure across the pulmonary vascular bed from the formula:

$$\text{PVRLLL} = 80 \times (\text{mean PAP} - \text{mean LAP}) \times \dot{Q}\text{LLL}^{-1}\ (\text{dyn s cm}^{-5}).$$

Hypoxic challenges were repeated at least five times until a steady state was established.

After obtaining control data for LLL hypoxia, the same experimental sequence was repeated after a 10-µg kg^{-1} bolus and constant infusion of nicardipine at 1, 3 and 6 µg kg^{-1} min^{-1} i.v. in sequence. Measurements of cardiopulmonary parameters were performed 20 min after commencing each infusion regimen when cardiovascular variables were in a steady state. Drug infusions were given during LLL normoxia and continued while the animal was rendered hypoxic. The duration of each infusion was 40 min, with an interval of 10 min between regimens. Body temperature was maintained at approximately 37.5 °C throughout the study.

As nicardipine 3 and 6 µg kg^{-1} min^{-1} significantly increased cardiac output, in seven dogs hypoxic responses with nicardipine were determined at constant cardiac output (controlled cardiac output group). A balloon catheter was placed in the inferior vena cava via the left femoral vein and cardiac output was maintained at the same value as the control LLL normoxia measurement by stepwise inflation of the balloon 10 min before measurement of LLL normoxia. Heparin 100 u kg^{-1} was administered i.v. before insertion of the balloon catheter and 50 u kg^{-1} i.v. was repeated at 2-h intervals.

Results are shown as means ± SEM. Data were analysed by within-subject analysis of variance for repeated measurements and Duncan's new multiple range test was applied when the significance of the analysis of variance reached a P value < 0.05.

RESULTS

Uncontrolled cardiac output

Heart rate (HR), PAP, mean PAP−LAP,

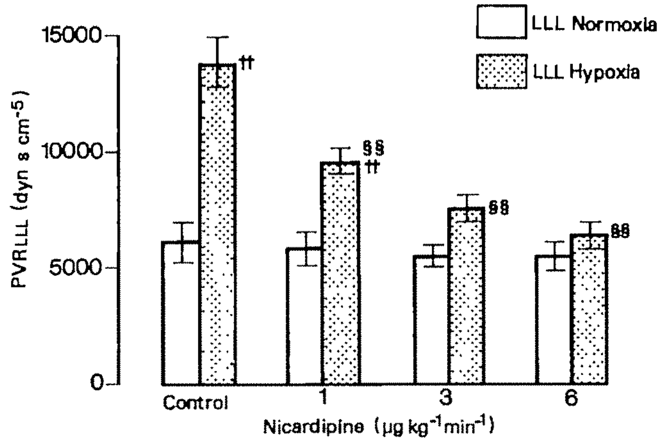

FIG. 2. Pulmonary vascular resistance of LLL (PVRLLL) during LLL normoxia and LLL hypoxia with and without nicardipine 1, 3 or 6 μg kg^{-1} min^{-1}. Mean ± SEM ($n = 7$). Significant change from LLL normoxia at same dose of nicardipine: ††$P < 0.01$. Significant change from control LLL hypoxia: §§$P < 0.01$.

PVRLLL and arterial blood-gas data remained almost unchanged during LLL normoxia (tables I, II). CVP varied between 3 and 5 mm Hg and LAP between 5 and 6 mm Hg, these variations being insignificant. Nicardipine 1–6 μg kg^{-1} min^{-1} significantly reduced mean AP (MAP) and systemic vascular resistance (SVR) while total lung PVR decreased by only a small and insignificant extent. $\dot{Q}$t increased significantly with the administration of 3 and 6 μg kg^{-1} min^{-1} compared with control values of LLL normoxia, and $P\bar{v}_{O_2}$ increased in accordance with $\dot{Q}$t, but this was not statistically significant. The plasma concentrations of nicardipine at different dose ranges were measured in four animals. There was no significant difference in the concentrations between LLL normoxia and LLL hypoxia at each rate of infusion of nicardipine (table II).

Before administration of nicardipine, hypoxic ventilation of the left lower lobe resulted in a significant decrease in $\dot{Q}$LLL/$\dot{Q}$t and Pa_{O_2} and a significant increase in PVRLLL. There was a small, insignificant change in total lung PVR (PVRt). A decrease in $\dot{Q}$LLL/$\dot{Q}$t and increase in PVRLLL with LLL hypoxic exposure were attenuated by nicardipine in a dose-dependent manner. $\dot{Q}$LLL/$\dot{Q}$t and PVRLLL did not differ between LLL normoxia and LLL hypoxia with infusion of nicardipine 3 and 6 μg kg^{-1} min^{-1} (table I, fig. 2). The percentage decrease in $\dot{Q}$LLL/$\dot{Q}$t and increase in PVRLLL were diminished significantly with the infusion of 3 μg kg^{-1} min^{-1} (fig. 3).

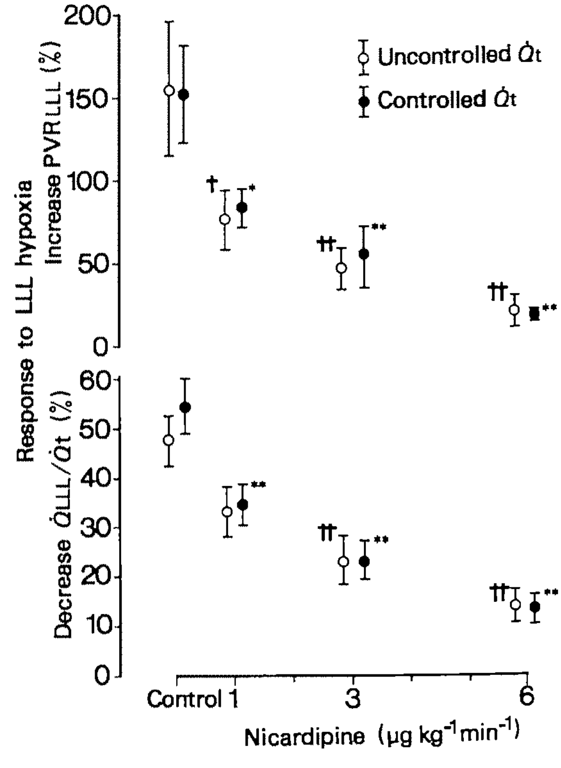

FIG. 3. Comparison of HPV response with nicardipine between uncontrolled and controlled cardiac output group. Mean ± SEM ($n = 7$). Differences from control values: †$P < 0.05$: ††$P < 0.01$: *$P < 0.05$; **$P < 0.01$.

TABLE I. *Effects of nicardipine on haemodynamic variables during LLL normoxia (N) and hypoxia (H) with uncontrolled cardiac output (mean ± SEM;* n = 7*). Significant change from control LLL normoxia:* *$P < 0.05$; **$P < 0.01$. *Significant change from control LLL hypoxia:* §$P < 0.05$; §§$P < 0.01$. *Significant change from LLL normoxia at same dose of nicardipine:* †$P < 0.05$; ††$P < 0.01$

		Nicardipine (μg kg^{-1} min^{-1})		
	Control	1	3	6
HR (beat min^{-1})				
N	136±10	138±5	140±7	142±8
H	142±6	138±4	137±6	132±10
MAP (mm Hg)				
N	115±7	87±3**	76±3**	69±3**
H	112±6	89±2§§	77±2§§	71±2§§
$\dot{Q}$t (litre min^{-1})				
N	1.18±0.05	1.22±0.04	1.48±0.09*	1.73±0.12**
H	1.16±0.04	1.24±0.05	1.5±0.1§	1.71±0.14§§
MPAP (mm Hg)				
N	22±2	20±1	21±1	23±2
H	25±2	22±1	23±1	23±2
MPAP−MLAP (mm Hg)				
N	16±2	15±1	16±2	17±2
H	19±3	17±1	17±1	17±2
SVR (dyn s cm^{-5})				
N	7875±620	5564±421**	4061±399**	2928±320**
H	7789±563	5644±427§§	4107±414§§	3090±325§§
PVRt (dyn s cm^{-5})				
N	1069±158	978±78	870±76	792±68
H	1271±174	1113±427	935±91	818±70
PVRLLL (dyn s cm^{-5})				
N	6018±884	5792±732	5377±504	5455±649
H	13807±1162††	9567±535§§††	7629±463§§	6318±449§§
$\dot{Q}$LLL/$\dot{Q}$t (%)				
N	18.4±1.5	18.0±2.2	16.5±2.1	15.5±2.2
H	9.7±1.3††	11.5±1.0†	12.4±1.2	13.1±1.5
Decrease in $\dot{Q}$LLL/$\dot{Q}$t (%)	47.8±5.5	33.7±5.4	23.5±4.8**	14.2±3.4**

TABLE II. *Effects of nicardipine on blood-gas variables (mean ± SEM;* n = 7*) during LLL normoxia (N) and hypoxia (H). The serum concentration of nicardipine after each administration is also indicated* (n = 4). *Significant change from control LLL normoxia:* **$P < 0.01$. *Significant change from control LLL hypoxia:* §§$P < 0.01$. *Significant change from LLL normoxia at same dose of nicardipine:* ††$P < 0.01$

		Nicardipine (μg kg^{-1} min^{-1})		
	Control	1	3	6
Pa_{O_2} (kPa)				
N	23.9±0.5	22.8±0.8	21.6±1.1	22.3±0.8
H	9.6±0.9††	9.6±0.9††	9.2±0.9††	9.5±0.9††
Pa_{CO_2} (kPa)				
N	4.8±0.1	4.7±0.1	4.5±0.1	4.7±0.1
H	4.9±0.1	4.7±0.1	4.7±0.1	4.8±0.1
$P\bar{v}_{O_2}$ (kPa)				
N	5.3±0.3	5.2±0.3	5.9±0.4	6.4±0.5
H	4.3±0.3	4.5±0.3	5.3±0.3	5.3±0.4
Serum concentration of nicardipine (ng ml^{-1})				
N		8.2±3.8	43.3±10	100.2±19.3**
H		9.8±4.3	45.8±10.5	113.3±20.7§§

TABLE III. Effect of nicardipine on haemodynamic parameters during LLL normoxia (N) and hypoxia (H) at constant cardiac output. Significant change from control LLL normoxia: *P < 0.05; **P < 0.01. Significant change from control LLL hypoxia: §P < 0.05; §§P < 0.01. Significant change from LLL normoxia at same dose of nicardipine: †P < 0.05; ††P < 0.01

	Control	Nicardipine (μg kg^{-1} min^{-1}) 1	3	6
HR (beat min^{-1})				
N	167±9	157±6	159±6	158±7
H	164±9	154±7	161±7	155±10
MAP (mm Hg)				
N	111±4	85±6**	68±7**	55±6**
H	110±4	88±5§	70±7§§	53±7§§
$\dot{Q}$t (litre min^{-1})				
N	1.53±0.10	1.49±0.12	1.5±0.13	1.52±0.14
H	1.56±0.17	1.47±0.13	1.52±0.15	1.51±0.16
MPAP (mm Hg)				
N	24±1	24±1	26±2	26±2
H	26±1	26±2	28±1	27±1
MPAP−MLAP (mm Hg)				
N	19±1	19±2	22±2	22±2
H	22±1	22±1	24±2	22±1
SVR (dyn s cm^{-5})				
N	5970±513	4566±499*	3599±386**	2739±235**
H	5890±581	4858±523	3697±401§§	2887±259§§
PVRt (dyn s cm^{-5})				
N	1033±142	1030±140	1181±151	1130±117
H	1125±134	1187±169	1296±208	1169±131
PVRLLL (dyn s cm^{-5})				
N	5034±831	5050±836	6134±1007	5907±1184
H	11893±1784††	8992±1292†	8030±1235§	6993±1384§
$\dot{Q}_{\mathrm{LLL}}/\dot{Q}$t (%)				
N	23.1±2.4	23.7±3.3	24.2±3.6	24.0±4.0
H	10.0±0.93††	14.6±1.2†	17.8±2.2	20.4±3.0§
Decrease in $\dot{Q}_{\mathrm{LLL}}/\dot{Q}$t (%)	54.7±5.5	35.5±4.1**	23.7±4.0**	13.1±2.8**

TABLE IV. Effect of nicardipine on blood-gas variables during LLL normoxia (N) and hypoxia (H) at constant cardiac output. Significant change from LLL normoxia at same dose of nicardipine: †P < 0.05; ††P < 0.01

	Control	Nicardipine (μg kg^{-1} min^{-1}) 1	3	6
Pa_{O_2} (kPa)				
N	23.6±0.4	22.8±1.2	23.5±0.5	22.4±0.8
H	9.9±0.4††	9.2±0.5††	9.2±0.3††	9.5±0.5††
Pa_{CO_2} (kPa)				
N	4.7±0.1	4.8±0.1	4.8±0.1	5.1±0.1
H	5.1±0.1	5.1±0.3	5.2±0.1	5.3±0.1
$P\bar{v}_{O_2}$ (kPa)				
N	6.0±0.3	6.0±0.1	6.3±0.1	6.3±0.1
H	5.2±0.3†	4.9±0.3††	5.5±0.3†	5.2±0.1††

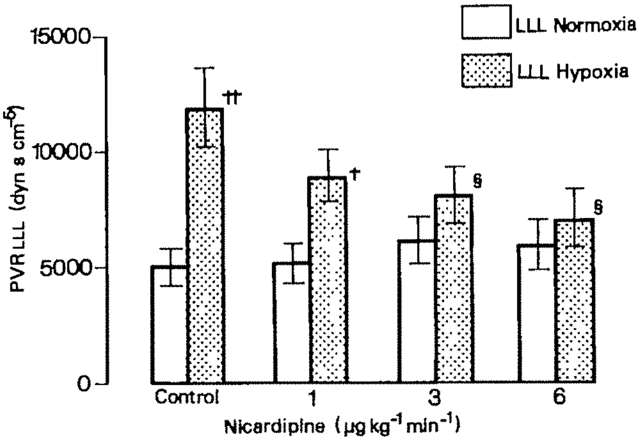

FIG. 4. Pulmonary vascular resistance of LLL (PVRLLL) during LLL normoxia and LLL hypoxia with and without nicardipine at constant cardiac output. Mean ± SEM ($n = 7$). Significant change from LLL normoxia at same dose of nicardipine: †$P < 0.05$; ††$P < 0.01$. Significant change from control LLL hypoxia: §$P < 0.05$.

Controlled cardiac output

$\dot{Q}$t was maintained at almost the same value as the control measurement for LLL normoxia (table III). $P\bar{v}_{O_2}$ during either LLL normoxia or LLL hypoxia was constant throughout the study, but was decreased significantly by LLL hypoxic challenge at each drug regimen (table IV). Other systemic haemodynamic blood-gas variables were similar to those of the uncontrolled cardiac output group.

PVRLLL during LLL hypoxia decreased significantly with nicardipine 3 µg kg^{-1} min^{-1} (fig. 4) and $\dot{Q}$LLL/$\dot{Q}$t during LLL hypoxia increased significantly with 6 µg kg^{-1} min^{-1} compared with LLL hypoxia before nicardipine. The HPV responses were attenuated by nicardipine in a dose-dependent manner. The percentage decrease in $\dot{Q}$LLL/$\dot{Q}$t lessened significantly with a dose of 1 µg kg^{-1} min^{-1}, while the percentage increase in PVRLLL was attenuated with a dose of 3 µg kg^{-1} min^{-1}. The magnitude of HPV responses with nicardipine was almost identical to those of the uncontrolled cardiac output group (fig. 3).

DISCUSSION

While the exact mechanism of hypoxic pulmonary vasoconstriction has not been determined, it is known that both alveolar oxygen partial pressure and mixed venous oxygen tension are mainly responsible for this response [6, 7]. In addition, it is known that various factors such as cardiac output [8, 9] pulmonary artery pressure [5], $P\text{CO}_2$ [2, 10] temperature [11], repeated intermittent hypoxic challenges [12, 13] and the size of the hypoxic compartment [14] modify the response of HPV directly or indirectly. Therefore, these factors should be taken into account when studying the effects of nicardipine on HPV. Of these factors, special attention should be paid to the alveolar $P\text{CO}_2$ of the hypoxic segment, as this is known to have a marked effect on HPV [10]. Regional alveolar hypoxia causes a decrease in regional blood flow which results in a reduction of alveolar $P\text{CO}_2$, provided that minute ventilation remains constant; the decreased $P\text{A}_{\text{CO}_2}$ may depress HPV. Because of fluctuations in $\dot{Q}$LLL/$\dot{Q}$t during hypoxia, addition of 5% carbon dioxide to the inspired gas has been tried in an attempt to stabilize the hypoxic vasoconstrictive response [15]. Although we did not use carbon dioxide gas for ventilating the LLL in this study, a stable and adequate maximum HPV response was obtained within 10 min after each hypoxic challenge, and thus measurements were performed at 10-min intervals.

Repeated hypoxic challenges have been found either not to affect [16, 17] or to increase HPV [12, 13]. In an experimental preparation similar to the present study exposure of a lung lobe to repeated intermittent hypoxic challenges has been reported to increase the lobar HPV [12, 13]. To avoid this effect, we repeated hypoxic challenges at least five times to verify that the HPV responses were consistent and stable.

Vascular smooth muscle cells contract by the initiation of membrane depolarization or activation of receptor operated ion channels, both of which increase cytoplasmic calcium concentration [18]. Calcium may be supplied from the extracellular compartment or intracellular sarcoplasmic reticulum [19]. Nicardipine, a short-acting potent calcium-channel blocking agent, directly blocks contractile responses mediated by membrane depolarization and transmembrane Ca^{2+} influx [20]. Nicardipine has more potent effects on vascular smooth muscle than on cardiac muscle [21]. Our data indicate that nicardipine has more effect on systemic than on pulmonary vasculature during normoxia.

The increase in cardiac output produced by nicardipine may be attributed to diminished afterload and or sympathetic responses to systemic vasodilatation, as suggested by Kishi, Okumura and Furuya [22]. Nicardipine has been shown to have little effect on either receptor-operated ion channels or intracellular calcium stores *in vitro* [20]. Because nicardipine attenuated HPV in the present study, this suggests that HPV is dependent largely on the increased transmembrane Ca^{2+} conductance induced by direct hypoxic stimulation to smooth muscle cells.

The effect of cardiac output on HPV has been investigated by Schumacker and colleagues [8] and Domino and colleagues [9]. In these studies, HPV was tested on left whole lung by either induced atelectasis or hypoxic ventilation. It was reported that increase in cardiac output produced by opening arteriovenous fistulae in the systemic circulation caused an increase in hypoxic lung blood flow or venous admixture. In Domino's study, blood flow through the left lung during hypoxic ventilation increased from 18.8% to 25.4% when cardiac output was increased by 43%. This increase in flow to the hypoxic lung may be explained by an increase in both mixed venous oxygen tension and perfusion pressure [8]. In our uncontrolled flow study, cardiac output increased by 47% in response to nicardipine and it was difficult, therefore, to discount an effect of cardiac output on HPV. However, the degree of attenuation of HPV by nicardipine was not different between the uncontrolled and controlled flow studies so it is postulated that nicardipine acts directly on pulmonary vessels constricted by hypoxia.

Inhibition of HPV by nicardipine caused no detectable decrease in Pa_{O_2}, in spite of a constant FI_{O_2} to the remainder of the lung. This may be explained by the iso-shunt graph of Benatar, Hewlett and Nunn [23]. If blood flow through the LLL is regarded as venous admixture, a small increase of hypoxic lung blood flow causes only a small reduction of Pa_{O_2} when the inspired oxygen concentration is relatively low (FI_{O_2} 0.3–0.4). However, if the hypoxic region of lung is larger or the inspired oxygen tension is greater, oxygenation may be impaired by nicardipine.

There is some evidence that calcium antagonists also act on mast cells or basophils to inhibit release of vasoactive substances such as histamine and leukotrienes, which have been proposed as mediators of pulmonary vasoconstriction [24, 25], although there is some divergence of opinion on the role of mediators [26–28] and further studies are required.

In conclusion, we have shown that nicardipine attenuates regional hypoxic pulmonary vasoconstriction through a direct action on pulmonary vessels constricted by hypoxia.

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BREATHING SYSTEMS FOR USE IN ANAESTHESIA

Evaluation Using a Physical Lung Model and Classification

D. M. MILLER

The major problem encountered when trying to measure the minimum flow requirements of breathing systems in the clinical setting is that of obtaining objective and accurate quantitative measurements of "rebreathing". This is particularly important when one has to compare systems with similarity of performance.

To evaluate a breathing system the relationship between effective alveolar ventilation ($\dot{V}$A) and fresh gas flow ($\dot{V}$F) must be determined. "Effective alveolar ventilation" is the volume per minute of fresh gas which enters the alveoli (all gas entering being considered as a mixture of fresh and alveolar gas); it decreases when the FGF is reduced to a critical value which marks the onset of what is commonly referred to as rebreathing, or an increase in rebreathing.

The terms rebreathing and functional deadspace ventilation can cause confusion unless clearly defined. For example, rebreathing can be understood as the re-inhalation of alveolar gas to the alveolar compartment, in which case rebreathing is unavoidable because of the presence of alveolar gas in the airways at end-expiration. Authors referring to the onset of rebreathing for a particular breathing system at a certain fresh gas flow rate should, according to the above definition, refer to this circumstance as the onset of an *increase* in rebreathing. Consequently, to avoid ambiguity, the term "functional deadspace ventilation" is used in place of "rebreathing". This is defined as the inhalation of alveolar gas to the alveolar compartment. Alternatively, it may be defined as the minute volume of ventilation ($\dot{V}$E) less the effective $\dot{V}$A. Therefore, the onset of an increase in rebreathing is marked by the onset of an increase in functional deadspace ventilation.

SUMMARY

A lung model which measures effective alveolar ventilation is described and used to evaluate different breathing systems during simulated spontaneous ventilation. The model measures VD/VT ratios in relation to fresh gas flow and the characteristic shape of the resulting curve characterizes the particular breathing system. The various curves reflect the functional performance and, therefore, the flow requirements of the systems which have been reclassified accordingly. The classification described is based upon the structural arrangements which determine the flow patterns within the particular systems. The breathing systems compared during spontaneous ventilation were a circle "C" absorber system, the circle "C" without the absorber, the Mapleson A, B, C and D systems and a series of "enclosed" and modified Mapleson A systems and the modified Mapleson D or Bain system.

Apparatus deadspace may contribute considerably to functional deadspace ventilation, by an amount which is usually less than the water displacement volume of the apparatus deadspace. Functional apparatus deadspace, therefore, is that portion—in addition to the anatomical deadspace—which contributes to the total functional deadspace ventilation when high enough fresh gas flows are used to prevent the latter contributing to functional deadspace.

A lung model which measures effective $\dot{V}$A, and therefore total functional deadspace ventilation, is described. It has been used to measure VD/VT ratios in relation to a range of fresh gas flows for a number of different breathing systems during spontaneous ventilation.

From the results of this evaluation of breathing systems, a clear perspective on flow requirements

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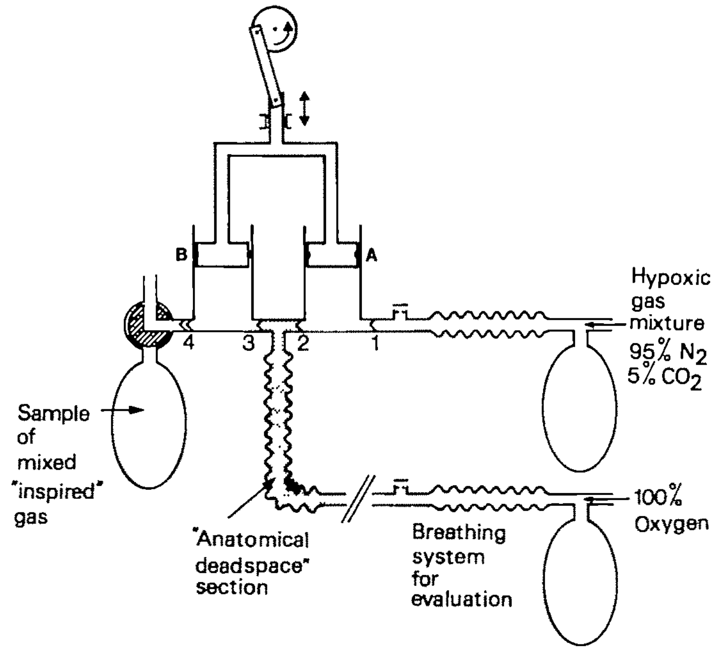

B
A
Hypoxic gas mixture
95% N_2
5% CO_2
4
3
2
1
Sample of mixed "inspired" gas
"Anatomical deadspace" section
Breathing system for evaluation
100% Oxygen

FIG. 1. A lung model which separates inspiratory from expiratory gas for the measurement of total functional deadspace. 1–4 = Valves. A = Expiratory portion of pump; B = inspiratory portion.

is ascertained for the various systems. These data, in conjunction with the literature on the use of breathing systems in controlled ventilation, are closely related to a proposed functional classification and recommended fresh gas flow requirements.

LUNG MODEL: DESCRIPTION AND METHODS

The lung model comprises an electric motor-driven pump which has two identical volume cylinders and pistons (fig. 1). The pistons are driven simultaneously and in the same direction in a close approximation to a sine-wave stroke. The cylinders are connected to a system of three one-way Rudolf valves plus a PEEP valve (No. 4) as shown in the diagram. The anatomical deadspace of the model is represented by the volume of the section between valves 2 and 3 and the connecting junction of the breathing system to be evaluated. The A section of the pump represents the expiratory portion and the B section the inspiratory portion. An anoxic gas mixture (in this case, a mixture of 5% carbon dioxide in nitrogen), is supplied at a flow rate in excess of the minute volume of the pump via a Magill breathing system to cylinder A. Only the anoxic mixture can be drawn into cylinder A via valve 1 during an inspiratory stroke and this is ejected during an expiratory stroke from cylinder A through valve 2 through the "anatomical deadspace" of the model and into the relevant breathing system. The breathing system is attached directly to the "anatomical deadspace" ($V\mathrm{D}^{\mathrm{anat}}$), as for tracheal anaesthesia. Pure oxygen (100%) is supplied as fresh gas through the breathing system. The effectiveness of the relevant system at removing the anoxic gas mixture (which represents expired alveolar gas) is then measured during the following inspiratory stroke of the pump.

The inspiratory stroke of the B cylinder results in valve 3 opening and what remains of the anoxic mixture in the $V\mathrm{D}^{\mathrm{anat}}$ and the breathing system mixed with the fresh gas (oxygen) is then aspirated through valve 3 into cylinder B. This mixture is collected in a large reservoir bag or Douglas bag after being expelled during an expiratory stroke through valve 4. A number of strokes of mixed inspired gas is analysed for oxygen and carbon dioxide concentrations. The $V\mathrm{D}/V\mathrm{T}$ ratio is then equal to the carbon dioxide concentration divided by 5, as 5% carbon dioxide was used. Alternatively, the same ratio is equal to $(100-O_2\%)/100$. The $V\mathrm{D}/V\mathrm{T}$ ratio could thus be measured in two ways, providing a means for confirming the validity of the results.

Oxygen was measured using a Godart paramagnetic Rapox analyser and was more precise than that of the measurement of the carbon dioxide, which was obtained using a Godart infrared analyser.

Different breathing systems were applied to the lung model, which was set to give a tidal volume of 397 ml at a rate of 17.5 "breaths" per minute, thus giving a minute volume of 6.95 litre min^{-1}. Starting with high flows, $\dot{V}_F$ was reduced and the respective V_D/V_T ratios were measured repeatedly until the values obtained were stable—that is until two identical readings were measured consecutively. The results were sufficiently precise and repeatable that more than two readings were deemed unnecessary. The functional anatomical deadspace (FADS) for the series of curves shown in figure 3 (Results) was 124 ml, giving a V_D/V_T ratio of 0.31. The FADS of the model was 174 ml for the curves shown in figure 4 (Results), giving a V_D/V_T ratio of 0.44. The water displacement volume of the anatomical deadspace was in fact 23 ml greater than the functional anatomical deadspace. The same tidal volume and ventilatory rate were used in both experiments.

Almost all the recorded measurements of V_D/V_T ratios were based on the oxygen values, and the carbon dioxide values were used as a back-up measurement and to allow verification. The reason for this was the finding that there was virtually no baseline shift during the experimental period using the oxygen analyser, whereas the capnograph required regular recalibration. When the circle absorption system was being evaluated, however, the measurements of carbon dioxide were used, having been verified against high flow measurements using oxygen. It should be apparent that the moment a fresh gas flow below the minute volume of ventilation was used with the "C" circle absorption arrangement [1], there was a discrepancy between V_D/V_T ratios measured by the two means. This reflected the activity of the soda-lime absorber, which came into play only at this flow rate.

Breathing systems evaluated in one series of experiments were: the Circle C arrangement absorber system made by Fraser-Sweatman; the Magill system made by British Oxygen Co.; the Humphrey ADE version of the Lack system using parallel tubes; the Penlon co-axial version of the Bain system, and two prototype enclosed-afferent reservoir systems, the details of which were described by Miller and Miller [2]. Another series compared the Mapleson D, the Bain, the conventional Mapleson C or Mapleson C afferent, the Mapleson C efferent, the Mapleson B and a modified Mapleson A system (fig. 2). The Mapleson C afferent is the conventional Mapleson C system with the fresh gas inlet nearer to the reservoir bag and the Heidbrink valve close to the patient. Swopping the position of the gas inlet and exit changes the system to a Mapleson C efferent version. The arrangements shown in figure 2 were used in order to retain the same T-piece throughout the experiment, hence the modified A arrangement.

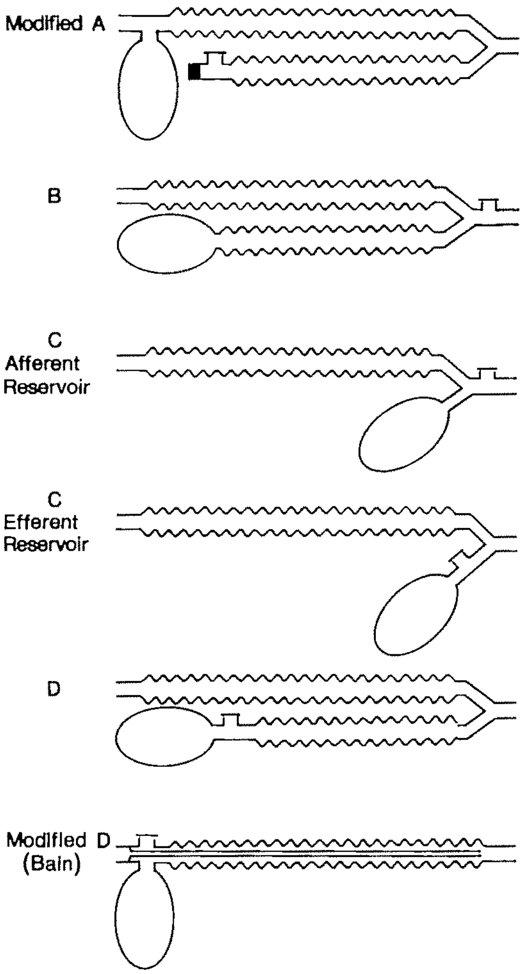


FIG. 2. The configuration of systems following Mapleson's classification of the functional characteristics which are shown in figure 3.

"Non-rebreathing" valve systems were not tested, for the obvious reason that the reservoir bag is simply emptied if $\dot{V}_F$ is less than $\dot{V}_E$.

Possible sources of error in the model include:

(a) Faults in the function of the Rudolf valves. These were carefully assessed for leaks and for delayed closure. Vertical positioning of the valves ensured proper closure with no back leak.

(b) Faulty operation of proper functioning valves is possible if there is an imbalance of pressures. For instance, a breathing system with a high opening pressure pop-off valve could cause fresh gas to flow through the breathing system at the end of the inspiratory phase and then through valves 3 and 4 if the pressure in the breathing system exceeds that in cylinder B. Therefore, an adjustable Siemens PEEP valve was inserted in series with valve No. 4 to ensure that no gas could escape through the latter, thus maintaining the pressure in the inspiratory side of the pump at the end of the inspiratory phase.

(c) Leaks in the system. A small leak in the cylinders was detectable at pressures greater than 20 cm H_2O. This was not considered to be significant, as the operating pressure of the model was well below that pressure.

(d) Nevertheless inspiratory and expiratory volume differed by a constant 3–5 ml per stroke, the latter giving the smaller volume. Many attempts to isolate the possible causes failed. The discrepancy was entirely related to the structural design of the model and was probably the result of a small difference in the stroke volumes of the two cylinders. As the purpose of this investigation was to compare different breathing systems under identical conditions this difference (of the order of 1 % of the tidal volume) was reasonably acceptable and should not have had any significant bearing on the comparison between the different systems.

RESULTS

The series of curves obtained when the V_D/V_T ratio was plotted against the fresh gas flow ($\dot{V}_F$) for all the major groups of breathing systems using the lung model (synonymous with spontaneous ventilation during tracheal anaesthesia) is shown in figures 3 and 4.

The circle carbon dioxide absorber system

As is to be expected for the circle absorption system, the performance was almost flow ($\dot{V}_F$) independent from 3 to 10 litre min^{-1}.

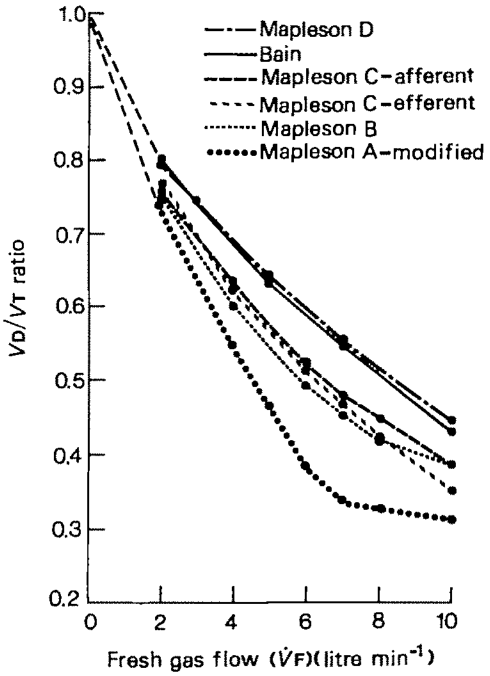


FIG. 3. The relation of fresh gas flow ($\dot{V}_F$) to V_D/V_T ratios for the Mapleson D, Bain, Mapleson C Afferent and Efferent, Mapleson B and Modified Mapleson A systems.

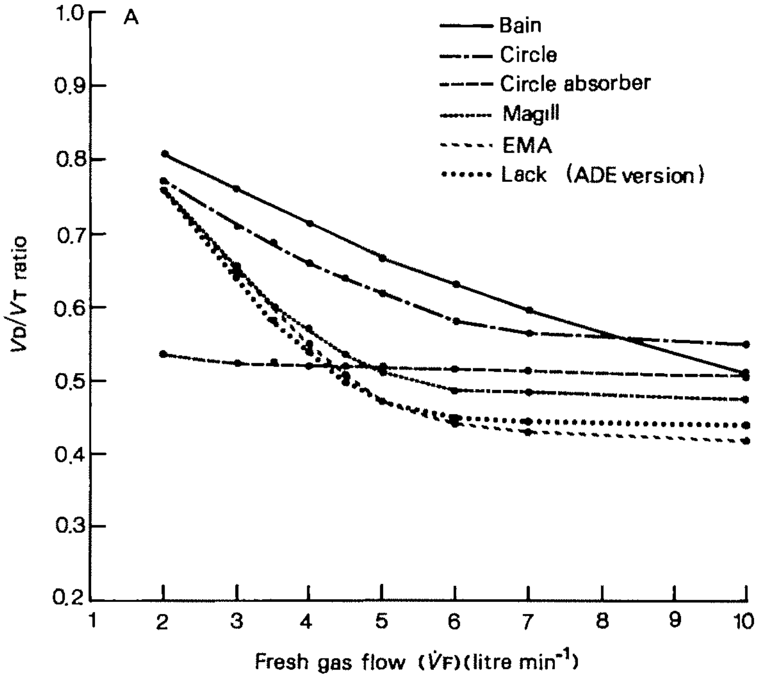
Non-absorber unidirectional flow systems

Two examples of a unidirectional flow system are the circle C, with and without the soda-lime cannister. An increase in V_D/V_T ratio was observed as soon as $\dot{V}_F$ was smaller than $\dot{V}_E$ for both systems.

This is demonstrated in figure 4B by the curves with the absorber switched in or out of circuit using the oxygen measurements for obtaining V_D/V_T ratios. A consistent increase in V_D/V_T ratio by 0.05 was noted which amounted to an increase in deadspace ventilation of 20 ml per tidal volume (397 ml) when the absorber was switched out of circuit.

Non-absorber bidirectional flow systems

Afferent. Afferent reservoir (AR) systems shown in figure 4 demonstrated the onset of an increase in V_D/V_T ratio when $\dot{V}_F$ decreased below 0.85 of $\dot{V}_E$, which was 6 litre min^{-1}. The rate of increase in the V_D/V_T ratio began to approach the maximum when $\dot{V}_F$ decreased below 0.72 of $\dot{V}_E$, which was 5 litre min^{-1}. This applied to the Magill, ADE version of the Lack and the Enclosed Mapleson A (EMA) systems. The Enclosed



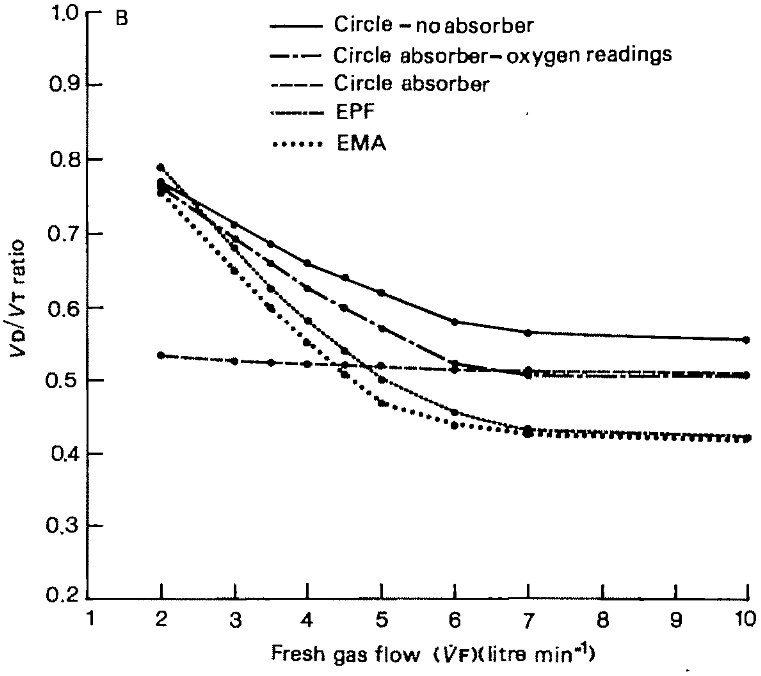


FIG. 4. A: The relation of fresh gas flow ($\dot{V}_F$) to V_D/V_T ratios for the Bain, circle without absorber, circle absorber, Magill, Lack and EMA systems. B: The relation of fresh gas flow ($\dot{V}_F$) to V_D/V_T ratios for the circle without absorber, circle absorber based upon oxygen measurements, circle absorber based upon carbon dioxide measurements, EPF and EMA systems.

Preferential Flow (EPF) system (a valveless version of an AR system) demonstrated a gradual increase in V_D/V_T ratios when $\dot{V}_F$ decreased to less than $\dot{V}_E$. This, as with the other AR systems, became maximal as soon as $\dot{V}_F$ decreased to less than 5 litre min^{-1}.

Efferent. The Bain *Efferent* Reservoir System showed an increase in V_D/V_T ratio throughout the range of $\dot{V}_F$ from 10 to 2 litre min^{-1} in figures 3 and 4A. The slope of this curve was significant throughout the clinical range of $\dot{V}_F$, even above 10 litre min^{-1}. No important difference was noted between the Bain and the classical Mapleson D system (fig. 3).

Junctional Reservoir Systems are shown in figure 3. The Mapleson B and two C system curves lie between the "pure" *Efferent* reservoir (Mapleson D and Bain) and *Afferent* reservoir (Mapleson A) systems. A Mapleson B *efferent* version was also evaluated, but for purposes of clarity was not included in the graph, since the result added no new information.

DISCUSSION

Ideally, a breathing system should be used during spontaneous ventilation on a zero gradient portion of the $\dot{V}_F:V_D/V_T$ ratio curve. Optimal flow requirements for a breathing system should, therefore, ensure sufficient fresh gas flow to achieve a zero or minimal gradient on the above mentioned curve. A gradient on this curve means that effective alveolar ventilation is not increased directly in relation to an increase in the minute volume of ventilation. Thus the likelihood of an imposed carbon dioxide load on breathing during clinical anaesthesia is increased. A substantial difference in the V_D/V_T ratios with the different systems using high fresh gas flows is clearly demonstrated and illustrates the difference in functional apparatus deadspace between the different systems.

For the circle C absorption system the curve remained practically horizontal throughout the tested range, as expected. Without the absorber in the circuit, the C circle curve remains horizontal when $\dot{V}_F$ is greater than $\dot{V}_E$. This agrees with the findings of Eger and Ethans [1]. Using the various AR systems, a $\dot{V}_F$ somewhere between $\dot{V}_A$ and $\dot{V}_E$ shows a significant change from the horizontal gradient which marks a decrease in alveolar ventilation. For the ideal AR system the turning point which marks an increase in deadspace ventilation should occur when $\dot{V}_F = \dot{V}_A$. In this study $\dot{V}_A$ was about 0.55 $\dot{V}_E$. The Magill, ADE and EMA systems were not as close to the ideal as one would expect. The EPF deviates even further from this ideal. Nevertheless, the predominant pattern of gas elimination reflects close similarities to the "pure" *afferent* reservoir systems which rely upon valves for flow direction.

The above results are not completely consistent with the conclusion of investigators who have evaluated these systems in the physiological state. A possible explanation for this is the fact that the effect of streaming as opposed to plug flow was perhaps more of a significant factor in the lung model than in the physiological state. In addition, and perhaps more importantly, methodological differences between clinical and laboratory studies would account for a more sensitive indicator of increased rebreathing with the latter techniques.

Humphrey [3] has reported that the Lack system had a fresh gas flow requirement 21 ml kg^{-1} min^{-1} less than that of the Magill system. In the present investigation, however, there was no difference in $\dot{V}_F$ requirements between the Humphrey ADE version of the Lack and the Magill system. There was, however, a difference in functional deadspace which was attributed to the different angle pieces used in the two systems. This amounted to 13 ml in this experiment. These findings concur with Conway's [4] conclusions that methodological differences relating to experimental technique account for Humphrey's findings.

In the case of the Bain system, a significant gradient on the $\dot{V}_F:V_D/V_T$ ratio curve is present even at a $\dot{V}_F$ of 10 litre min^{-1}, which is about 1.5 $\dot{V}_E$. Meakin and Coates [5] demonstrate that, during anaesthesia, when $\dot{V}_F$ is less than 2 $\dot{V}_E$ "rebreathing" results; yet they recommend a $\dot{V}_F$ equal to the awake minute volume ($\dot{V}^{tot}$), which is about 1.5 $\dot{V}_E$. The logic behind this conclusion is based on the assumption that the resulting rebreathing is unimportant. This investigation shows that, when $\dot{V}_F$ is equal to 1.5 $\dot{V}_E$, the functional deadspace ventilation is equivalent to that of the circle absorber system used here and slightly greater than other afferent reservoir systems. In addition, the gradient of the curve figure 4A illustrates that $\dot{V}_F = 1.5$ $\dot{V}_E$ is less than optimal. It should be re-emphasized, however, that the flow requirement of a breathing system in spontaneous ventilation is concerned with maximizing effective alveolar ventilation or minimizing deadspace ventilation. Additional deadspace ventilation imposes a load upon breathing when using less than optimal flows, and this is not acceptable. Our criteria for acceptability should not be survival, but what is best for the patient. For the Bain system, therefore, a fresh gas flow of 100 ml kg^{-1} min^{-1}—as recommended by Bain and Spoerel [6]—is well below optimal flows. $\dot{V}_F$ in the Bain system should be at least 2 $\dot{V}_E$ to ensure sufficient effective alveolar ventilation during spontaneous ventilation with tracheal anaesthesia. This conclusion is in line with the recommendations of Mapleson [7], Conway, Seeley and Barnes [8], Ungerer [9], Rose, Byrick and Froese [10] and Byrick [11]. For use in children, the minimum flow used should be 3 $\dot{V}_E$, according to Lindahl, Charlton and Hatch [12].

In figure 2, the two Mapleson C arrangements referred to are the *afferent* C, which is the usual arrangement with the expiratory valve proximal to the patient and the fresh gas inlet distal to the valve, and the *efferent* C, in which these are reversed. The flow requirements and gaseous elimination pattern are virtually the same. The *efferent* system demonstrates a smaller functional anatomical deadspace than the conventional C system. The same finding was obtained with an *efferent* B system (not shown). The Mapleson B system was a slight improvement as regards fresh gas economy, possibly because of marginally better compartmental storage of deadspace gas in the blind reservoir bag limb. Nevertheless, for all three systems shown which could be referred to as neither efferent nor afferent reservoir systems, but junctional reservoir systems, the estimated flow requirements for spontaneous ventilation should exceed 1.5 $\dot{V}_E$.

Apparatus deadspace appears to play a significant role in determining effective alveolar ventilation. However, it does not appear to affect the characteristic flow requirements for the different systems. Flow requirements are determined more by the groups of breathing systems illustrated in the classification.

Additional interesting findings observed in figures 3 and 4, apart from the fresh gas flow requirements of the different systems, merit discussion. For example, the fractional utilization of fresh gas at a low fresh gas supply is illuminating as regards the functional performance of the different systems. For all systems which selectively shunt out alveolar gas when using a $\dot{V}_F \simeq \dot{V}_A$, all the $\dot{V}_F$ delivered, no matter how small, will reach the alveolar compartment and contribute to effective alveolar ventilation. The lower the $\dot{V}_F$, using the circle system without the absorber, the better the chance of recycling expired deadspace gas and, hence, the convergence of the circle system curves with those of the *afferent* reservoir curves as $\dot{V}_F$ is reduced. Also, for the Bain system, as the $\dot{V}_E/\dot{V}_F$ ratio approaches infinity (when $\dot{V}_F = 0$), a proportional increase in the utilization of fresh gas occurs. Under normal circumstances in the Bain system, fresh gas occupying the anatomical deadspace at the end of inspiration is virtually never recycled.

The difference between the circle C arrangement using oxygen measurements, with the absorber in or out of circuit, illustrates two different types of circle C systems. The oxygen measurement with absorber in circuit illustrates a C system in which the absorber cannister forms a large reservoir between the expiratory valve and the fresh gas inflow. This allows for the conservation of fresh gas during the expiratory phase. When the absorber is switched out of circuit, fresh gas is lost through the expiratory valve during expiration with the *afferent* unidirectional valve held closed. The volume of fresh gas lost occurs in a direct relation to the fresh gas flow. As the fresh gas flow decreases, the difference between the two circle C arrangements diminishes. This explanation has been confirmed in the laboratory using different circle system arrangements applied to the same lung model.

FUNCTIONAL CLASSIFICATION

A classification should aid understanding rather than become an exercise in semantics, as illustrated by the eight different classifications using such terminology as closed, semi-closed, semi-open and open [13–20].

Table I classifies breathing systems on the basis of structure and function, both of which have a direct bearing on the performance characteristics with regard to fresh gas flow. The manner in which the system is used has no influence upon this classification and, in this way, the ambiguities inherent in previous classifications are avoided.

As Conway [4] has already pointed out, there should be two broad classes of breathing systems: those which use a means for the absorption of carbon dioxide and those which do not.

Each of these classes can then be subdivided

TABLE I. *Functional classification*

			Description
SYSTEMS WITH ABSORPTION OF CARBON DIOXIDE			
(i) *Unidirectional*—circle arrangements			Sword (1930) [21]
(ii) *Bidirectional*—To & Fro Cannister			Waters (1924) [22]
SYSTEMS WITHOUT THE ABSORPTION OF CARBON DIOXIDE			Functional description
	Minimal $\dot{V}_F$ requirement		
(i) *Unidirectional flow*			
(a) Non-rebreathing valves	Spontaneous	Controlled	
	1 $\dot{V}_E$	1 $\dot{V}_E$	Rubin, Laerdal, Fink, Ambu and others (in [23])
(b) Circle systems	$1+\dot{V}_E$	1 $\dot{V}_E$	Eger and Ethans (1968) [1]
(ii) *Bidirectional flow*			
(a) Simple Afferent Reservoir	Spontaneous	Controlled	
Magill			Magill (1928) [24]
Lack	0.7–1 $\dot{V}_E$	2 $\dot{V}_E$	Lack (1976) [25]
P.F.			Miller (1979) [26]
(b) Enclosed Afferent Reservoir			
EMA, EPF	0.7–1 $\dot{V}_E$	0.7 $\dot{V}_E$	Miller and Miller (1988) [2]
(c) Junctional Reservoir			
Mapleson B and C	$1.5+\dot{V}_E$	1.5 $\dot{V}_E$	Mapleson (1954) [7]
(d) Efferent Reservoir			
Bain	2–3 $\dot{V}_E$	1 $\dot{V}_E$	Bain and Spoerel (1972) [6]
Mapleson D,			Mapleson (1954) [7]
E,			Ayre (1937) [27]
F			Jackson Rees (1950) [28]

into unidirectional and bidirectional flow systems. For the absorber systems this subdivision is of little consequence as regards the fresh gas flow requirements. However, for the non-absorber systems, fresh gas flow requirements do differ considerably and the details of these differences are discussed under separate headings.

Non-absorber systems

In *unidirectional flow systems* gas movement can flow only in one direction past the patient T-piece connector. This is usually achieved by means of two unidirectional flow valves (e.g. circle absorber systems) or by using non-rebreathing valves (e.g. Ambu, Fink, Rubin, Laerdal and many others [23]). Relating the flow requirements to the various circle arrangements was described by Eger and Ethans [1] and is not a simple matter.

Bidirectional flow systems are subdivided into *afferent* and *efferent* reservoir systems, depending upon which limb of the breathing system allows for the predominant to-and-fro movement of gas.

The *afferent* tube is the one supplying fresh gas from the anaesthetic machine to the patient. For there to be to-and-fro movement in this limb, there has to be a reservoir facility (e.g. a reservoir bag) in the afferent limb, hence the term Afferent Reservoir systems. The afferent reservoir makes it possible for deadspace gas to be stored during the expiratory phase of spontaneous ventilation and for alveolar gas to be selectively eliminated when a fresh gas flow rate ($\dot{V}_F$) between the alveolar minute volume ($\dot{V}_A$) and the minute volume of ventilation ($\dot{V}_E$) is used.

Afferent reservoir (AR) systems can be subdivided into simple and enclosed afferent reservoir (EAR) systems. The hallmark of all AR systems, as mentioned above, is the selective elimination of alveolar gas in spontaneous ventilation. The distinction between enclosed and simple AR systems is noted in controlled ventilation. The EAR systems during controlled ventilation retain the efficient shunting of gas fractions that occurs in spontaneous ventilation, making the flow requirements a fraction of that required by the simple AR systems in controlled ventilation. In addition, the fresh gas flow requirement of the EAR systems is even less than the efferent reservoir systems during controlled ventilation [2]. On the other hand the flow dynamics of simple AR systems during controlled ventilation are completely different from spontaneous ventilation. The gas eliminated from the system is identical in composition, although not in volume, to the inspired gas, as gas is eliminated via the valve during the inspiratory phase. The minimum recommended flow requirement is, therefore, estimated at 1.5 to 2 times the basal $\dot{V}_E$.

Concerning the Mapleson B and C systems, Mapleson [7] has stated that they have little to commend them. The reason for this is that placement of the reservoir bag close to the junction of the afferent and efferent limbs results in a marked reduction in the compartmental storage capacity of fresh gas. Considered as an afferent reservoir system, the compartmental storage capacity is as small as the volume between the fresh gas inlet and the expiratory valve. If one were to transpose the position of the inlet and the expiratory valve then, technically, one would have an afferent reservoir system with the compartmental storage facility of negligible volume. The functional difference between these differing arrangements is indeed small (fig. 3). These systems can thus be described as *junctional reservoir systems*, with the disadvantages of both afferent and efferent reservoir systems and the advantages of neither as regards economy of fresh gas in both spontaneous and controlled ventilation. The reason for this is that the reservoir bag acts as a mixing chamber, with minimal, or no, chance of compartmental storage of the different gas fractions because of the junctional siting of the reservoir bag.

The *efferent* tube is the one carrying predominantly expired gases from the patients to the exhaust or scavenging port. For to-and-fro movement to occur in this limb, the reservoir can consist of the expiratory tube open to the atmosphere (e.g. Mapleson E) or Mapleson D and F arrangements in which, in addition to the efferent tube, a reservoir bag is attached. Perhaps it is here that the terms referring to "openness" or "closedness" of a system may form a relevant part of the description. Nasal spectacles, for example, is an "open" efferent reservoir (ER) system, the reservoir being the nose or nares and the atmosphere. A Ventimask is not quite as "open", the mask having a larger volume than the nares. The gradation of openness to enclosure varies between nasal spectacles, Ventimask, Mapleson E, Mapleson F and Mapleson D. The important thing, however, is that for all efferent reservoir systems, during spontaneous ventilation, the minimum fresh gas flows to prevent an increase in deadspace ventilation are of a moderate to high flow range, that is from $2\dot{V}_E$ to the peak inspiratory flow [5, 7–9, 11, 12, 29].

However, for controlled ventilation, the criterion for flow requirements is normocarbia, as the work of breathing is done by the ventilator. There is ample evidence to show that, with hyperventilation, $\dot{V}_F$ need be only 70 ml kg^{-1} min^{-1} to achieve normocarbia in the Bain system [30–32]. This is equal to the usual minute volume of ventilation during anaesthesia with spontaneous ventilation.

All bidirectional flow systems can be used with high flows, defined as a flow equal to or exceeding the peak inspiratory flow rate. Under these circumstances all systems function as unidirectional flow systems. Nevertheless, one must bear in mind that it is breathing systems which are being classified and not the manner in which they are being used. It is the kind of breathing system which determines the minimum fresh gas flow which will ensure adequate effective alveolar ventilation. The relationship of the different groups to fresh gas flow requirement fulfills the necessary ingredient for a classification called for by Hamilton [33].

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PROPOFOL FOR ARTHROSCOPY IN OUTPATIENTS

Comparison of Three Anaesthetic Techniques

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AND R. DONADONI

Propofol in emulsion formulation (Diprivan) is an anaesthetic agent which may be given by continuous i.v. administration. As it is short acting, propofol might be useful in day-case surgery. However, minimal analgesic properties require its use in combination with an analgesic agent.

The aim of the present study was to assess the acceptability of combining propofol with alfentanil or nitrous oxide for arthroscopy in day-case patients. Comparison was made with a technique in which anaesthesia was maintained with isoflurane after induction with propofol. Assessments were made of cardiovascular and respiratory variables, craniobiopotentials (SEMG, EEG) and recovery characteristics (Trieger test, deletion of *p* test).

PATIENTS AND METHODS

This study involved 60 unpremedicated outpatients (ASA grade I or II; aged 18–60 yr; weight 45–80 kg) undergoing arthroscopy. The study was approved by the Ethics Committee of the hospital and informed consent was obtained from each patient.

Two detection electrodes and one standard electrode were applied fronto-temporally to register frontal EMG (and EEG) using the Anaesthesia Brain-activity Monitor (ABM Datex): spontaneous EMG activity (SEMG) was expressed in arbitary units (0–100). Heart rate (HR) was derived from ECG lead II, and arterial pressure (AP) was monitored continuously (Dinamap). A respiration monitor (Normocap Datex) was used to measure ventilatory rate (RR) and end-tidal carbon dioxide ($P\text{A}_{CO_2}$).

SUMMARY

Sixty unpremedicated adult patients, undergoing arthroscopy, received propofol 2 mg kg^{-1} for induction of anaesthesia, before random allocation to three groups receiving one of the following: a continuous infusion of propofol supplemented with nitrous oxide in oxygen (group I); isoflurane and nitrous oxide in oxygen (group II); a continuous infusion of propofol in combination with repeated bolus doses of alfentanil (group III). The results showed no major differences in cardiovascular variables between the groups. Ventilation rate was highest in group II. Early recovery was less smooth and showed slight impairment in group III compared with the other groups. The data suggest that induction of anaesthesia with propofol followed by maintenance with isoflurane or continuous infusion of propofol is preferable for this procedure.

Assessments of HR, AP, RR, $P\text{A}_{CO_2}$ and SEMG were made before induction, during anaesthesia (5, 10, 15, 20 and 30 min), at the end of the procedure, and on awakening. For practical reasons, rate of ventilation was monitored only in the first part of the study. Recovery tests (deletion of *p* and Trieger tests) were performed before induction and 30, 60 and 180 min after the end of anaesthesia.

In all patients, anaesthesia was induced with propofol 2 mg kg^{-1} given over 20 s into a fast-running i.v. infusion of 0.9% saline via an antecubital vein. Patients were allocated randomly to three groups of 20. In group I, an infusion of propofol was started immediately after induction at an initial rate of 12 mg kg^{-1} h^{-1} which was reduced to 9 mg kg^{-1} h^{-1} after 30 min. The patients breathed a mixture of nitrous oxide in

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TABLE I. *Demographic data, ASA I or II patients undergoing arthroscopy (mean ± SEM)*

	n	Age (yr)	Weight (kg)	Sex (M/F)	Duration of procedure (min)	Time interval between start of induction and surgery (min)
Group I	20	33±3	67±2	11/9	56±4	13.2±2
Group II	20	27±3	66±2	10/10	63±4	15.5±3
Group III	20	30±3	67±1.9	13/7	51±4	13.6±3

TABLE II. *Number of patients in each group responding with reactions at incision*

	Group I (*n* = 20)	Group II (*n* = 20)	Group III (*n* = 20)
SEMG increase to > 60 at incision	10	9	12
Movement at incision	8	9	8

oxygen (2:1) spontaneously by mask. In group II, patients breathing spontaneously by mask received 1.3% isoflurane and 66% nitrous oxide in oxygen, decreased to 1% after 30 min. In group III, a bolus of alfentanil 7 μg kg^{-1} was given after induction, followed by an infusion of propofol at a rate of 12 mg kg^{-1} h^{-1} for 30 min, and 9 mg kg^{-1} h^{-1} thereafter. The patients breathed air. Increments of alfentanil 7 μg kg^{-1} were given when SEMG exceeded 60 units.

Statistical analysis was performed by the Friedman two-way analysis of variance and the Kruskal–Wallis one-way analysis of variance by ranks.

RESULTS

There were no statistical differences between the three groups for age, weight, sex, duration of the procedure, or the time interval between start of induction and surgery (table I).

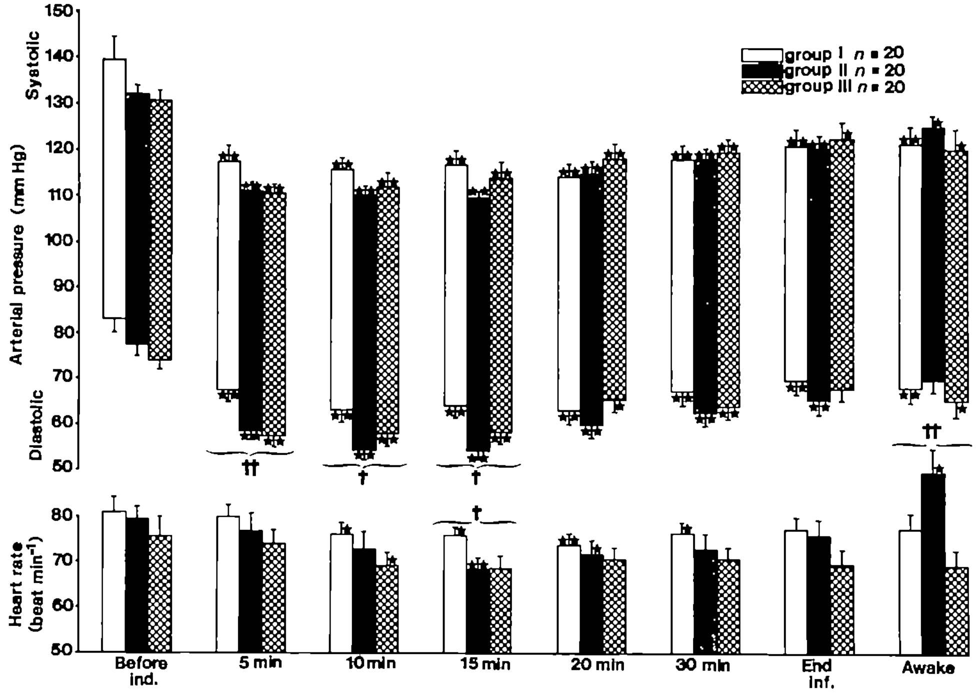

FIG. 1. Cardiovascular changes in the three groups. Significant differences: *$P < 0.05$, **$P < 0.02$ compared with before induction; †$P < 0.05$, ††$P < 0.02$ between groups.

Induction of anaesthesia with propofol 2 mg kg^{-1} was smooth in all patients and characterized by a sudden decrease in SEMG. In 31 patients there was an abrupt increase in SEMG at the start of surgery, accompanied, in some, by movement of a limb (table II). They were nearly equally allocated between the three groups. These patients received a supplement of propofol 0.5 mg kg^{-1}.

Cardiovascular changes are shown in figure 1. After induction of anaesthesia, a statistically significant decrease in systolic arterial pressure was noted in all groups at all assessment times during anaesthesia ($P < 0.02$) and on awakening ($P < 0.05$). There was no statistical difference between the three groups. While systolic arterial pressure remained constant during established anaesthesia, the decrease in diastolic arterial pressure ($P < 0.02$) was most pronounced during the first 15 min after induction. Highest values were recorded in group I (intergroup difference $P < 0.05$). There was a moderate decrease in heart rate which was most pronounced in group II (isoflurane) after 15 min and in group III throughout the procedure. In group II, heart rate increased ($P < 0.05$) on awakening (intergroup difference $P < 0.02$).

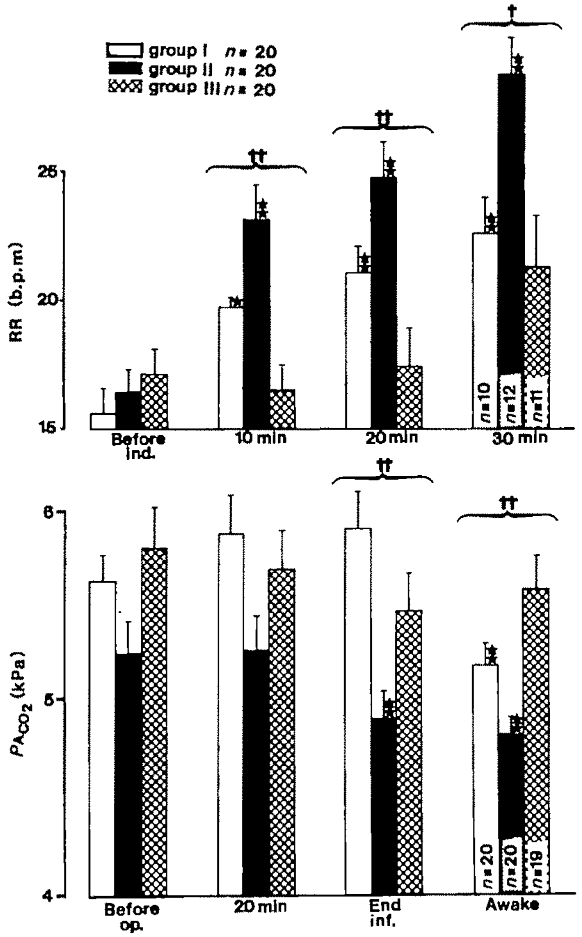

FIG. 2. Changes in rate of ventilation (RR) and $P_{A_{CO_2}}$ in the three groups. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.02$ compared with before induction; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.02$ between groups.

Respiratory changes are shown in figure 2. After induction and during maintenance of anaesthesia, ventilatory rate increased most in group II ($P < 0.02$), moderately in group I ($P < 0.05$) and remained nearly stable in group III (intergroup difference $P < 0.02$ at 10 and 20 min and $P < 0.05$ at 30 min). Throughout the procedure, $P_{A_{CO_2}}$ values remained constant in group III. At the end of the procedure they decreased ($P < 0.02$) in group II. Apnoea followed induction in two patients in group I, seven in group II and five in group III. The duration was less than 15 s in all except two patients who received alfentanil and who required assisted ventilation for more than 5 min.

In all patients in groups I and II, SEMG remained low (10–15 % of the initial value) during infusion and increased when consciousness was regained. In group III, however, increases in SEMG (to more than 60) occurred during anaesthesia and four additional bolus doses of alfentanil were given (mean total dose 22 µg kg^{-1}).

After anaesthesia, 7 min elapsed in group I before the SEMG reached a value of 70. This was significantly longer ($P < 0.02$) than in the other groups (group II 4 min, group III 4.5 min). Recovery time, however, measured as the interval

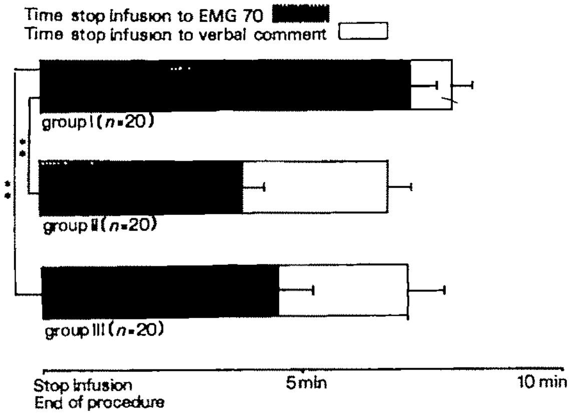

FIG. 3. Recovery times (mean ± SEM) in the three groups. $^{**}P < 0.02$.

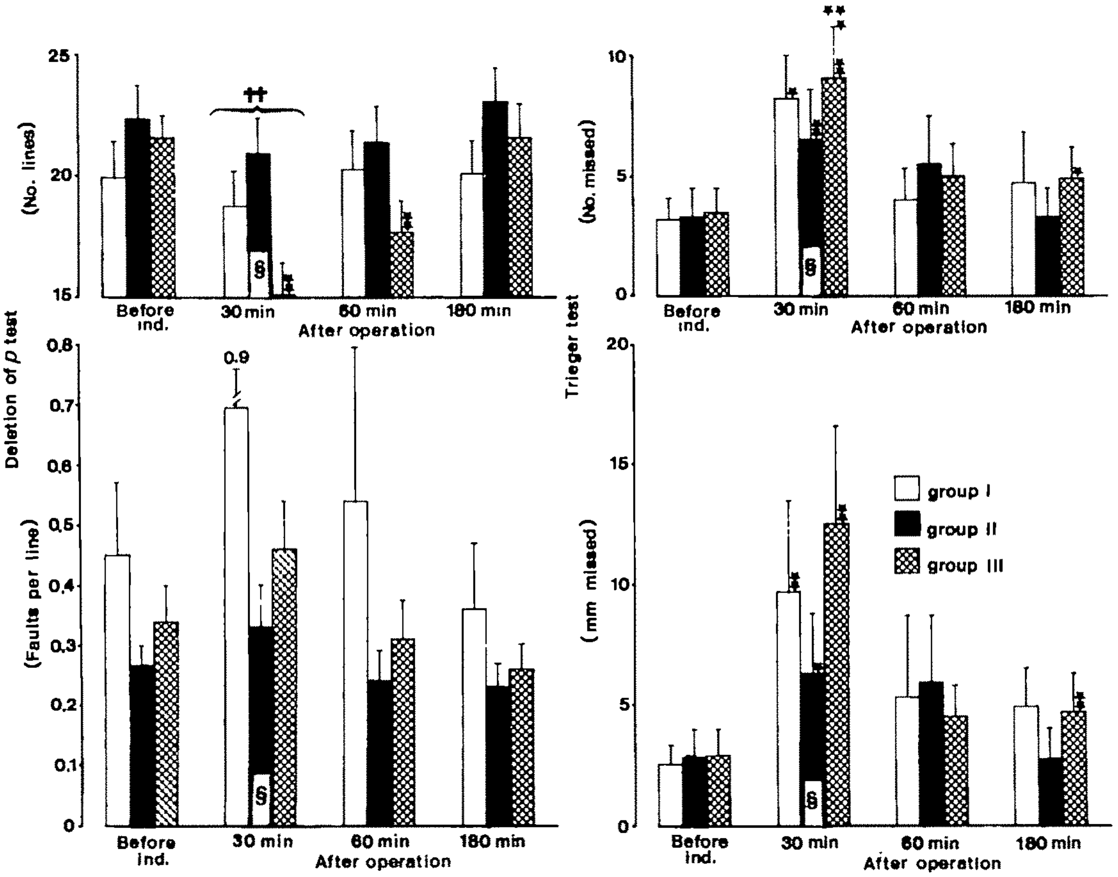

FIG. 4. Recovery tests (mean ± SEM) in the three groups ($n = 20$; except §$n = 18$). Significant differences: *$P < 0.05$, **$P < 0.02$ compared with before induction; ††$P < 0.02$ between groups.

from the end of anaesthesia to the response to a verbal command was similar in all groups (fig. 3).

There was no significant difference between the three groups in the performance of the Trieger and deletion of *p* tests before anaesthesia. At 30 min after anaesthesia, however, two patients in group II were unable to perform the tests. At 30 and 60 min, patients in group III showed impaired performance in the deletion of *p* test compared with baseline and particularly in comparison with patients in groups I and II (inter-group difference at 30 min $P < 0.02$). Baseline values were attained only after 180 min. In group I, there was a wide distribution of results for the errors per line, and again baseline values were obtained only at 180 min.

In the Trieger test, all groups showed statistically significant impairment at 60 min after anaesthesia compared with baseline values. Only for group III patients did impairment remain statistically significant after 180 min (fig. 4).

During the first 60 min after anaesthesia, nausea and vomiting occurred in three patients in group I and four in group II. Three patients in group III elected to stay overnight in hospital, because of delayed occurrence of nausea and vomiting or feeling unwell. Dreams described as pleasant were reported by four patients in group I, three in group II and three in group III.

DISCUSSION

This study was undertaken to evaluate three techniques of anaesthesia for arthroscopy in outpatients. Day-case anaesthesia requires safety, adequate levels of anaesthesia, predictability, rapid recovery and minimal side effects. The three different techniques used short-acting drugs in combination to provide anaesthetic and analgesic properties.

Although propofol 2 mg kg^{-1} is reported to be an appropriate induction dose [1, 2], in the present study 50% of patients showed an increase in SEMG after surgical incision and, in some, this was accompanied by movement. In unpremedicated patients, an induction dose of propofol 2.5 mg kg^{-1} may be more appropriate, as suggested by other investigators [3].

Haemodynamic changes in the three groups were acceptable. Arterial pressure showed a similar moderate decrease in each group. However, the central vagotonic effect of propofol, in combination with alfentanil, might allow slower heart rates to occur with lower arterial pressure [4].

Frequently, a short period of apnoea occurs after induction of anaesthesia with propofol [3, 5], but assisted ventilation is not required. However, induction with propofol in the presence of alfentanil may produce apnoea lasting some minutes. Two patients in the present study required temporary assisted ventilation. This has been reported to occur under similar conditions by other investigators [6].

During surgery, there was an increase in the rate of ventilation which was most pronounced in the isoflurane group. Although tachypnoea was present in the isoflurane group, neither clinical judgement nor the SEMG, indicated inadequate anaesthesia. In this group, Pa_{CO_2} values showed the greatest decrease, although they remained within a safe and acceptable range for spontaneously breathing patients.

A sensitive measurement of an adequate depth of anaesthesia is a low spontaneous EMG value. If the level of anaesthesia is inadequate, an increase in SEMG occurs before alterations in heart rate, arterial pressure and ventilatory rates are noted. In groups I and II, SEMG remained stable at a low value. By contrast in group III, SEMG increased to values exceeding 60 at various times during anaesthesia. On each occasion, values decreased in response to the administration of a bolus dose of alfentanil 7 μg kg^{-1} and remained at a low level for 5–15 min.

After anaesthesia, SEMG values reached 70 in group I more slowly than in the other groups ($P < 0.05$). This may suggest that the deepest level of anaesthesia is achieved by the technique used in this group. However, there was no significant difference in total recovery time between the groups. Thus despite a seemingly deeper level of anaesthesia in group I, recovery was rapid.

To avoid disturbing the normal recovery process, only two tests of vigilance were performed. Two patients in the isoflurane group were unable to perform these tests. This could be caused by the concentration of isoflurane used [7]. Patients in group III recovering from a technique involving propofol and alfentanil showed impaired performance in the deletion of *p* test at 30 and 60 min and in the Trieger test at 180 min. Patients in group I showed a wide pattern of distribution during the first 60 min. Although vomiting and nausea were not seen during the early recovery period, three patients stayed in hospital overnight because of delayed nausea.

In conclusion, several factors suggest that the combination of propofol and alfentanil is less appropriate for outpatient anaesthesia than the two other techniques. These include the occurrence of prolonged apnoea after induction, delayed nausea and vomiting, a slower return to full recovery and an unpredictable depth of anaesthesia. The combination of an infusion of propofol and nitrous oxide is a preferable technique. This is safe, predictable, provides a fast recovery and is associated with an acceptable incidence of side effects.

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NITROUS OXIDE AND DAY-CASE LAPAROSCOPY: EFFECTS ON NAUSEA, VOMITING AND RETURN TO NORMAL ACTIVITY

P. SENGUPTA AND O. M. PLANTEVIN

SUMMARY

Patients admitted for day-case laparoscopy were assigned randomly to receive nitrous oxide–oxygen or oxygen, with enflurane, during a standard anaesthetic technique. Postoperative morbidity, in particular nausea and vomiting, and ability to resume normal activity were assessed over the ensuing 48 h. Supplementary administration of propofol during the operative procedure was required significantly more often ($P < 0.05$) in the absence of nitrous oxide. There was no significant difference in the incidence of vomiting before discharge when nitrous oxide was omitted. The incidence and severity of nausea over the 48 h following operation was similar in both groups. There was no difference in analgesic or anti-emetic requirements before discharge and the time taken to resume normal activity was similar. It is concluded that nitrous oxide may be avoided readily in day-case laparoscopy without affecting postoperative morbidity or time taken to return to "street fitness" and normal activity.

Alexander and colleagues [1] found that nitrous oxide appears to reduce the frequency of postoperative nausea and vomiting after gynaecological laparoscopy, although the duration of effect was not documented. Lonie and Harper [2] found also, in patients undergoing laparoscopy, a significantly reduced incidence of postoperative vomiting, still evident the day after operation, when nitrous oxide was omitted from the anaesthetic technique, but there was no difference in the incidence of nausea. The frequency of nausea and vomiting after day-case laparoscopy may exceed 80% [3] and might affect the patient's ability to resume normal activity. This study was designed to assess primarily the effect of nitrous oxide on nausea and vomiting and subsequent return to normal activity after day-case laparoscopy.

PATIENTS AND METHODS

Eighty unpremedicated patients older than 18 yr and ASA status I/II were assigned randomly to receive nitrous oxide–oxygen or oxygen as part of a standard anaesthetic technique for day-case laparoscopy. Patients with a history of excessive nausea and vomiting after previous anaesthetics were excluded.

All anaesthetics were administered by the authors. The patients were given fentanyl 1.5 μg kg^{-1} i.v. and anaesthesia was induced with propofol 2 mg kg^{-1} i.v. followed by vecuronium 0.06 mg kg^{-1} i.v. Propofol was chosen because of its short elimination half-life (35–60 min), having been shown to be superior as an induction agent to both methohexitone and thiopentone with respect to immediate postoperative recovery in day-case surgery [4]. The patient's lungs were ventilated manually using a Guedel airway for 2 min before tracheal intubation, which was accomplished after the vocal cords had been sprayed with 4% lignocaine; one group received an inspired gas mixture of 33% nitrous oxide and 1% enflurane in oxygen, and the other 2% enflurane in oxygen. Thereafter ventilation was maintained with a Bain system and a Nuffield Penlon ventilator. The Bain system was arranged with a side-arm through which metered air from a cylinder could be mixed with the gases emerging from the outlet of the Boyle's machine. A Critikon

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Oxychek oxygen analyser was sited distal to the air inlet and a Hewlett–Packard 47210A capnometer was used to measure end-tidal carbon dioxide concentrations. The ECG was monitored by Cardiorator CR5 on standard lead 2 and the heart rate recorded at 5-min intervals. The incidence and type of any arrhythmias were noted. Arterial pressure was measured at 5-min intervals using an Accutorr ultrasonic recorder, and an Engstrom Emma analyser was used to monitor end-tidal enflurane concentration.

In theatre, the inspired enflurane concentration was adjusted to give the group receiving nitrous oxide an end-tidal concentration of 0.75% and the second group an end-tidal concentration of 1.5%. In the group not receiving nitrous oxide, ventilation was maintained with 40% oxygen-enriched air using a fresh gas flow of 70 ml kg^{-1}, a frequency of 12 b.p.m. and a tidal volume adjusted to maintain the end-tidal carbon dioxide concentration within the normal range. Movements by the patient during laparoscopy, lachrymation, sweating and a heart rate greater than 100 beat min^{-1} or a systolic arterial pressure greater than 20 mm Hg in excess of the preoperative value recorded on two consecutive occasions were criteria for giving increments of propofol.

All laparoscopies were performed by the same operator. Approximately 2 litre of carbon dioxide was used to insufflate the peritoneum. Sterilizations were excluded from the study. At the end of the procedure attempts were made to remove as much carbon dioxide from the peritoneal cavity as possible and neuromuscular block was antagonized with atropine 1.2 mg and neostigmine 2.5 mg i.v. Pharyngeal suction was carried out before tracheal extubation if possible, and the airway removed immediately thereafter.

Patients were transferred to a recovery area and prescribed paracetamol 500 mg by mouth 4-hourly as required for pain and metoclopramide 10 mg i.m. as required for nausea and vomiting. I.m. pethidine was available if necessary for severe pain. The incidence and frequency of vomiting and administration of analgesic and antiemetic drugs were recorded. Patients were asked to grade nausea and abdominal pain as nil, mild, moderate or severe 30 min after admission to recovery and every 1 h thereafter until discharge, which occurred when the patient was considered to be "street fit" (when they were alert and orientated, with stable recordings of heart rate and arterial pressure, and able to ambulate normally, unaided).

On discharge patients were given a questionnaire to be completed at 24 and 48 h after operation. Nausea, abdominal pain and backache were graded as absent, mild, moderate or severe and appetite was graded as absent, below normal or normal. Inquiries as to abdominal pain were included because of possible association with emetic symptoms and those as to backache and tiredness so that patients' attention would not be focused unduly on nausea and vomiting.

Statistical analysis was performed by Chi-square with Yates' correction.

RESULTS

We studied 80 patients, of whom 64 (80%) (33 in the nitrous oxide group and 31 in the second group) returned questionnaires; analysis was undertaken, therefore, on 64 patients. There were no significant differences between the groups in age, weight, duration of anaesthesia or surgery (table I). There was a small number of arrhythmias, but arterial pressure and heart rate remained stable throughout the procedure in both groups. In the nitrous oxide group, three patients developed bradycardia requiring atropine and two developed a nodal rhythm which did not require treatment. In the group not receiving nitrous oxide, two patients developed bradycardia requiring atropine and two had nodal rhythms which did not require treatment. Supplementary bolus injections of propofol were administered

TABLE I. *Age, weight and duration of anaesthesia, surgery and stay in the recovery room before discharge in patients receiving either nitrous oxide–oxygen or oxygen. Mean values (range)*

	Nitrous oxide	Without nitrous oxide
Age (yr)	31.13 (18–41)	31.32 (22–61)
Weight (kg)	60.88 (37.2–80.7)	61.62 (47.2–83.0)
Duration of anaesthesia (min)	23.87 (16–44)	22.10 (16–33)
Duration of surgery (min)	14.83 (9–26)	14.64 (10–26)
Duration of stay in recovery (h)	3.6 (2–6)	3.4 (2–6)

TABLE II. *Postoperative morbidity and administration of analgesic and anti-emetic drugs before discharge (number of patients per group). No significant difference between groups*

		Nitrous oxide	No nitrous oxide
Nausea	Severe	5	3
	Moderate	7	7
	Mild	5	4
	Total	17	14
	Nil	16	17
Vomiting	> 2	0	0
	× 2	5	1
	× 1	6	3
	Total	11	4
	0	22	27
Abdominal pain	Severe	4	7
	Moderate	21	12
	Mild	6	10
	Total	31	29
	Nil	2	2
Analgesia	I.m.	2	2
	Oral	27	19
	Nil	4	10
Anti-emetic		13	10
Awareness		0	1

toward the end of the procedure in eight patients (26 %) not receiving nitrous oxide to prevent slight movements, compared with one (3 %) in the nitrous oxide group ($P < 0.5$).

One patient only, who did not receive nitrous oxide, complained of awareness. This patient remembered hearing voices for a short period during laparoscopy but, on direct questioning afterwards, did not complain of any discomfort or regard the experience as distressing. There were no significant differences after operation in the incidence or severity of nausea, vomiting or abdominal pain. Frequency of administration of anti-emetics and oral analgesics were similar (table II).

Analysis of the returned questionnaires revealed no significant differences in emetic symptoms. At 24 h after operation 51.5 % complained of nausea and 18 % complained of vomiting in the nitrous oxide group, compared with 38.7 % and 9.7 %, respectively, in the second group. At 48 h the frequencies were 30.3 % for nausea and 9.1 % for vomiting in the nitrous oxide group, compared with 25.8 % and 0 %, respectively, in the second group. Abdominal pain, backache, appetite and time taken to resume normal activity were similar in both groups over the 48 h following discharge.

DISCUSSION

The omission of nitrous oxide from an anaesthetic technique has been reported to reduce emetic symptoms following in-patient gynaecological laparoscopy [1, 2]. The emetic effect of nitrous oxide may result from opioid receptor agonism [5–7], pressure effects in closed body cavities, or both. Studies have shown that the incidence of nausea after day-case laparoscopy varies between 36 and 82 % during immediate postoperative recovery [3, 8], approaches 28 % 24 h after discharge [8, 9] and 11 % 48 h after discharge [9]. The incidence of vomiting before discharge is reported to vary between 11 and 49 % [2, 10].

Our results are consistent with these data, but we found that the use of nitrous oxide did not increase the frequency of emetic sequelae. These findings are not so unequivocal as those of Alexander, Skupski and Brown [1] who demonstrated a significant reduction in both nausea and vomiting on omission of nitrous oxide, but tend to support the results of Lonie and Harper [2]. However, although our study has not demonstrated a statistically significant difference in the incidence of postoperative vomiting, 33 % of the nitrous oxide group vomited compared with 12.9 % of the second group in the immediate postoperative period. If this trend were to persist, sample sizes of approximately 100 patients per group would have been necessary to have sufficient power to produce a statistically significant result at the 0.05 % level.

Previous experience in our unit has shown that, with 67 % nitrous oxide and fentanyl 1.5 μg kg^{-1} i.v., 0.75 % enflurane provides good anaesthetic conditions for day-case laparoscopy. During induction, higher concentrations of enflurane were used in both groups to prevent possible awareness during this vulnerable period. Nitrous oxide reduces MAC for enflurane by approximately 60 %. When it was omitted for simplicity, the enflurane concentration was doubled. However, the total MAC for the group not receiving nitrous oxide was therefore slightly less than for the nitrous oxide group, which might explain the significantly greater use of bolus injections of propofol in the former group and the single case of awareness (table II). Nonetheless, the case of awareness and the 26 % incidence of movement when nitrous oxide was omitted suggests that nitrous oxide may confer some advantages for the production of smoother anaesthesia and thereby compensates for its tendency to increase postoperative emetic symptoms, especially as these do not seem to delay discharge and resumption of normal activity. Use of slightly greater concentrations of enflurane during laparoscopy, when nitrous oxide is omitted, should reduce the incidence of awareness and movement. The absence of effect on discharge time is supported by other studies [11].

Although linked to postoperative emetic symptoms, appetite is also an indicator of general wellbeing and was included in the questionnaire to detect any subtle differences between the groups. However, no differences were observed between the two groups.

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PERIOPERATIVE CHANGES IN FUNCTIONAL RESIDUAL CAPACITY IN MORBIDLY OBESE PATIENTS

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SUMMARY

Functional residual capacity (FRC) was measured before and after induction of anaesthesia for jejunoileal bypass surgery in 30 morbidly obese patients. The onset of anaesthesia was associated with a 51% reduction in FRC from 2.2 litre to 1.0 litre. Eighteen of the patients were investigated more extensively; in these subjects FRC was reduced below the control values of residual volume (RV) with the onset of anaesthesia, but recovered towards baseline after laparotomy incision. Reduction in FRC is related to baseline vital capacity (VC) and FRC and is much greater than that reported for patients of normal weight.

A reduction in FRC following induction of anaesthesia occurs in normal subjects [1]. However, little is known of variations in FRC in morbidly obese patients undergoing general anaesthesia. Don and colleagues [2] described a negative relationship between FRC during anaesthesia (expressed as percent of preanaesthesia values) and the weight:height ratio. This relationship predicts a marked decrease in FRC for obese patients, but in morbidly obese patients investigated before and after induction of general anaesthesia a reduction in FRC was found lower than that observed in patients of normal weight [3].

The present study has investigated the effect of general anaesthesia and muscle paralysis on FRC (as measured by the helium dilution technique) in obese patients; FRC changes produced by laparotomy were also investigated.

PATIENTS AND METHODS

Eighteen normocapnic morbidly obese patients (group A) of mean weight 152 kg (table I) undergoing jejunoileal bypass surgery were studied after informed consent had been obtained. The day before anaesthesia respiratory function tests were performed, including FRC, RV, VC and FEV_1, in the supine position.

Measurement of FRC was also undertaken at 5 min before and after induction of anaesthesia and after the laparotomy incision (approximately 20 min after induction of anaesthesia). FRC was measured also in seven of these patients during anaesthesia, full muscle paralysis and mechanical ventilation, after the skin incision was closed (approximately 3.5 h after induction of anaesthesia).

Twelve additional patients were studied (group B: mean weight 127 kg (table I)), although measurements were confined to determination of FRC immediately before and after induction of anaesthesia.

In all patients, after premedication with atropine 0.5 mg i.m. and methadone 10 mg i.m., anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., neuromuscular blockade was produced with suxamethonium 1 mg kg^{-1} and tracheal intubation performed under direct laryngoscopy. Anaesthesia was maintained with fentanyl 3.5 µg kg^{-1} and droperidol 50 µg kg^{-1}.

Maintenance of neuromuscular blockade was with pancuronium 0.04 mg kg^{-1} first bolus and 0.015 mg kg^{-1} every 30 min. Enflurane 1% and 50% nitrous oxide were added to the inspired gas mixture only after completion of the FRC measurements following laparotomy in order to avoid interference with the helium analyser [4]. After skin closure 30 min was allowed to elapse

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TABLE I. *Demographic data*

Patient No.	Age (yr)	Weight (kg)	Height (cm)	Sex	Smoker?	Weight (% of ideal)
Group A						
1	49	158	185	M	No	181
2	36	182	175	M	No	237
3	47	189	168	M	No	264
4	39	137	163	F	Yes	231
5	37	135	169	F	No	212
6	49	145	169	F	Yes	220
7	39	150	150	F	Yes	286
8	42	115	166	F	Yes	179
9	53	172	174	M	No	223
10	38	205	185	M	Yes	238
11	44	181	176	M	No	231
12	35	106	148	F	Yes	207
13	46	101	162	F	No	164
14	46	196	178	M	Yes	246
15	33	159	165	F	No	262
16	43	120	180	M	Yes	146
17	43	154	160	F	No	255
18	55	133	166	F	Yes	201
Mean	43	152	169			221
SD	6	31	10			37
Group B						
1	27	130	164	F	Yes	220
2	35	161	150	F	No	308
3	52	95	165	F	No	145
4	35	129	150	F	No	247
5	37	107	162	F	No	181
6	37	110	159	F	No	191
7	34	132	158	F	No	232
8	50	150	168	M	No	208
9	34	110	169	M	No	154
10	29	141	175	F	Yes	211
11	48	117	165	F	No	184
12	36	145	162	F	No	245
Mean	38	127	162			211
SD	8	20	7			45

after discontinuing nitrous oxide and enflurane before FRC was measured again.

The patient's lungs were ventilated mechanically using a Kontron ABT 4100 ventilator and non-rebreathing system, with a tidal volume of approximately 7 ml kg^{-1} (equivalent to 14.7 ± 4 ml kg^{-1} if body weight were ideal), ventilatory rate of 16 b.p.m. and an $F_{I_{O_2}}$ of 0.5 throughout the procedure.

FRC measurement

FRC measurements in duplicate were obtained in the supine position on the day before anaesthesia, using classic closed-circut helium dilution method and also with a simplified technique [5].

The simplified method comprised an anaesthesia bag filled with 2 litre of a gas mixture consisting of 13% helium in oxygen; the bag was connected to the lungs at the end of expiration and 15 deep manual ventilations performed. The final helium concentration (He_{fin}) in the anaesthesia bag was measured with a helium analyser and FRC computed according to the formula:

$$FRC = V_i(He_i/He_{fin}) - V_i$$

Where V_i is the initial gas volume in the anaesthesia bag, and He_i and He_{fin} are the initial and final helium concentrations, respectively, in the anaesthesia bag.

The simplified method was used for all subsequent FRC measurements.

Statistics and computation

The ideal body weight was obtained from the Build study tables [6]. The extent of obesity was standardized using the body mass index (BMI, kg m^{-2}) obtained by dividing the weight by the (height)^2.

The predicted FRC anaesthesia:FRC preanaesthesia ratio [2] was calculated from the equation:

$$\frac{\text{FRC during anaesthesia}}{\text{FRC before anaesthesia}} \times 100 = 137.7 - 164.4\ \frac{\text{weight (kg)}}{\text{height (cm)}}$$

Results are expressed as mean ± SD. Analysis of the results was made using Student's t test for paired data and least squares regression analysis as required. A probability value of less than 0.05 was considered significant.

RESULTS

In both groups FRC decreased by 51% after induction of anaesthesia and muscle paralysis: from 2.2 ± 0.8 litre to 1.0 ± 0.3 litre ($P < 0.01$).

There were no differences in FRC reduction between smokers and non-smokers and between males and females. The "Don equation", derived originally from patients of normal weight, did not predict the data in our morbidly obese patients (predicted FRC anaesthesia:FRC preanaesthesia ratio −2.7 ± 26%). However, we found a positive correlation between the FRC anaesthesia:FRC preanaesthesia ratio and BMI ($P < 0.01$).

TABLE II. *Obese patients (group A). Preoperative spirometric and blood-gas data. VC = Vital capacity; FEV_1 = forced expiratory volume in the first 1 s; FRC = functional residual capacity as measured with a closed circuit helium dilution method; RV = residual volume—data not available*

Patient No.	VC (litre)	VC (% of ideal)	FEV_1/VC	FRC (litre)	RV (litre)	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)
1	3.78	61	59	2.67	2.63	—	—
2	3.22	59	65	1.98	1.76	6.1	8.6
3	2.35	50	81	1.94	1.94	5.4	8.5
4	3.03	77	88	2.32	2.10	5.3	13.0
5	3.97	90	82	2.46	2.06	4.3	14.6
6	3.43	80	82	1.75	1.71	4.7	11.87
7	2.48	81	76	1.94	1.76	4.9	12.0
8	3.52	85	76	2.12	2.06	5.1	10.8
9	4.43	87	76	2.74	2.42	4.9	10.2
10	4.31	67	83	3.17	2.86	4.9	14.5
11	3.82	70	80	3.19	3.01	5.7	9.7
12	2.72	92	77	1.00	0.73	5.3	11.5
13	2.59	68	84	1.45	1.27	5.1	12.4
14	3.36	60	82	1.79	1.74	7.0	9.5
15	2.91	71	83	1.62	1.26	5.5	11.2
16	4.24	73	80	2.91	2.73	—	—
17	3.19	79	74	1.40	1.27	6.1	12.1
18	2.22	56	82	1.65	1.60	6.0	10.3
Mean	3.31	73	78	2.12	1.94	5.9	11.3
SD	0.69	12	7	0.63	0.62	0.6	1.9

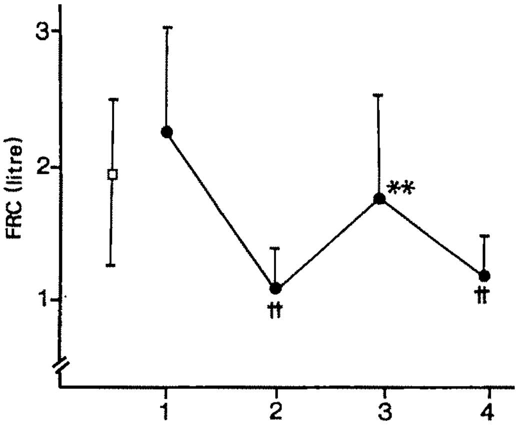

FIG. 1. Changes in FRC (●) throughout the study in group A (obese patient). The preoperative residual volume (□) is presented also for reference. Events: 1 = before induction, 2 = after induction of anaesthesia and paralysis; 3 = after laparotomy incision; 4 = after skin incision closure. †† $P <$ 0.01 compared with 1; **$P < 0.01$ compared with 2.

The decrease in FRC after induction of anaesthesia (FRC preanaesthesia − FRC after anaesthesia) correlated strongly with the preanaesthesia FRC values ($P < 0.01$).

TABLE III. *Changes in FRC throughout the study;* †† P < *0.01* v. *before induction (paired data);* **P < *0.01* v. *after induction (paired data). — Data not available*

Patient No.	Before induction (litre)	After induction (litre)	After laparotomy (litre)	After skin incision closure (litre)
Group A				
1	2.20	1.06	1.46	—
2	2.33	1.94	3.42	—
3	1.88	1.47	3.78	—
4	1.47	0.83	1.47	—
5	2.00	0.80	1.33	—
6	3.10	0.83	1.33	—
7	2.13	1.13	1.47	—
8	1.66	1.17	1.29	1.10
9	3.65	1.25	2.12	1.77
10	3.65	1.38	2.00	—
11	3.20	1.21	1.88	—
12	1.51	0.63	0.99	0.56
13	1.73	0.83	1.09	1.17
14	1.88	1.21	1.66	1.06
15	1.52	1.06	2.13	1.17
16	3.53	0.99	—	1.51
17	1.10	0.80	—	—
18	1.94	1.08	1.66	—
Mean	2.25	1.09††	1.82**	1.19††
SD	0.81	0.31	0.77	0.38
Group B				
1	1.50	0.57		
2	1.42	0.92		
3	3.10	0.92		
4	2.28	1.68		
5	2.55	1.25		
6	2.40	0.76		
7	2.71	0.55		
8	1.49	1.21		
9	2.88	0.92		
10	2.30	0.65		
11	1.99	0.77		
12	1.60	0.95		
Mean	2.18	0.93††		
SD	0.58	0.32		

Spirometric measurements (VC, FRC, FEV_1/VC, RV) in group A, obtained in the supine position the day before anaesthesia, are presented in table II. On this occasion, FRC was measured both with the classic helium dilution method and also with the simplified technique. Similar results were obtained (2.1 ± 0.6 litre *v.* 2.2 ± 0.6 litre, respectively, regression coefficient 1.02, $P < 0.01$).

Immediately after anaesthesia, FRC decreased to values lower ($P < 0.01$) than the initial value for RV (0.84 ± 0.6 litre less than the baseline RV).

The FRC reduction after anaesthesia was related to the VC ($P < 0.01$) and to the preanaesthesia FRC ($P < 0.01$) as observed in the overall population. However, following laparotomy incision, FRC returned to values (1.8 ± 0.8 litre) not significantly different from baseline.

After closure of the skin incision, FRC in seven patients during anaesthesia, full muscle paralysis and artificial ventilation was reduced (1.2 ± 0.4 litre in comparison with their preanaesthesia FRC values ($P < 0.01$). FRC measurements of different phases of the study are presented for both groups in table III and summarized for group A in figure 1, where RV values in supine position are also presented for reference.

DISCUSSION

We have found in morbidly obese patients that FRC decreased after induction of anaesthesia, to approximately 50% of preanaesthesia values.

A marked decrease in FRC after anaesthesia was predicted for obese patients [2]. However, our data suggest that the reduction in FRC after anaesthesia is relatively greater in obese than normal weight patients. Thus the equation described by Don and colleagues [2] to predict the reduction in FRC produced by anaesthesia cannot be applied to the obese population.

In agreement with previous studies, we have found that the reduction in FRC and VC occurred as a result of variable decreases in expiratory reserve and inspiratory reserve volumes. In morbidly obese patients in the supine position, the chest wall system is less compliant than normal, causing a decrease in total respiratory compliance [7].

It is likely that the patients with larger FRC and VC volumes before anaesthesia are those in whom the ventilatory muscles counteract more efficiently the encroachment on FRC. Removal of ventilatory muscle tone by anaesthesia and muscle paralysis, therefore, may cause a larger decrease in FRC.

While the FRC does not vary during the course of laparotomy in normal weight subjects [8,9], we observed a significant increase in FRC (almost back to preanaesthesia values) following the laparotomy incision. Appelgren, Panuska and Tsueda [10] have demonstrated a caudal displacement of the diaphragm after laparotomy in morbidly obese patients. A cranial shift of the diaphragm has been identified as a main factor causing reduction in FRC after induction of anaesthesia in normal weight patients [11].

In a previous study of 10 obese subjects undergoing anaesthesia, a reduction in FRC was found of only 10% [3]; however, it is not clear in this study if the FRC measurement (20 min after induction of anaesthesia) was obtained before or after the laparotomy incision. If the latter were the case, the difference between their data and those of the present study (obtained before laparotomy incision) may be explained.

The reduction in FRC occurring after induction to values less than the pre-anaesthesia RV is striking. Since RV represents the minimum volume that the chest wall–diaphragm system may reach, a further reduction in lung volume may be explained by a fluid (blood?) shift into the thorax [12]; compression of the vena cava has been described as a possible mechanism for such a shift of blood. If so, laparotomy incision may decrease the extent of vena caval compression and partially reverse this shift of blood.

The reduction in FRC to values below RV is not related to the method of FRC measurement, since Westbrook and co-workers [13] described this phenomenon in one of three anaesthetized subjects, using a volume displacement body plethysmograph. Also, Ford and others [14], studying 15 surgical patients in the postoperative period, found a reduction in FRC to values below the preoperative RV in three overweight patients.

It is known that airway closure may trap gas behind, thus sequestering a portion of lung volume from measurement by inert gas dilution. Should airway closure increase during anaesthesia, the FRC may be underestimated. However, the simplified method of measurement of FRC we have used provides large manually induced tidal volumes that should prevent gas trapping [8]. Furthermore, in the present study, FRC returned almost to baseline values after the laparotomy incision, suggesting that mechanisms other than gas trapping account for the observed reduction in FRC.

We conclude that, in obese patients in the supine position, FRC is reduced dramatically during general anaesthesia with muscle paralysis and mechanical ventilation, as a result of craniad shift of the diaphragm. We also speculate that further reduction in lung volume is probably caused by shift of blood into the thorax.

In view of the very low FRC reached after induction of anaesthesia in our obese patients, we suggest that the period of apnoea accompanying intubation is particularly hazardous and may account for some anaesthesia accidents reported in these patients [15]. We therefore support the suggestion [16] that intubation should be performed before induction of anaesthesia if possible.

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EFFECT OF NIFEDIPINE ON CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND INTUBATION

G. D. PURI AND Y. K. BATRA

Laryngoscopy and intubation cause hypertension, tachycardia and arrhythmias [1, 2] and attenuation of these changes is important in patients with coronary artery disease. Various attempts have been made to block this stress response, but most are only partially successful [3–7].

Calcium blocking drugs produce dilatation of both peripheral and coronary arteries [8]. The present study was designed to assess the efficacy of the calcium blocking agent nifedipine in attenuating the hypertensive response to laryngoscopy and intubation.

PATIENTS AND METHODS

The study was undertaken in 40 healthy normotensive patients (ASA grade I) in the age range 30–40 yr undergoing elective surgery. Informed consent was obtained in all instances. No patient was receiving sedative, anti-hypertensive or other medication likely to interfere with this study. The patients were allocated randomly to a control (n = 20) or nifedipine (n = 20) group.

Premedication consisted of diazepam 10 mg by mouth on the evening before surgery and also 2 h before induction of anaesthesia. In addition, all patients received morphine 0.2 mg kg^{-1} and promethazine 0.5 mg kg^{-1} 1 h before induction.

In the anaesthetic room, heart rate and arterial pressures (systolic, diastolic and mean) were recorded using an automatic monitor (Nippon Colin Co., Japan) and an i.v. infusion was commenced with 5% dextrose.

Patients were given sublingually, by the second author, either a nifedipine gelatine capsule (10 mg) or a placebo capsule of similar appearance (random allocation). ECG monitoring was instituted and 10 min after administration of the sublingual capsule, anaesthesia was induced with thiopentone 5.5 mg kg^{-1} over a period of 45 s, followed by suxamethonium 1.5 mg kg^{-1}. Laryngoscopy was attempted 60 s after suxamethonium and tracheal intubation was completed within 30 s in all patients. All intubations were performed by the first author, who was unaware of the nature of the sublingual capsule. Serial heart rate and arterial pressure measurements were obtained before and after induction, after administration of suxamethonium, immediately and 1, 2 and 3 min following laryngoscopy and intubation.

Anaesthesia was maintained with 70% nitrous oxide in oxygen; ventilation was spontaneous, assisted or controlled, as required. After tracheal intubation, ventilation was controlled using the same gas mixture delivered by a Servo ventilator (Siemens Elema 900 B) at a rate of 12 b.p.m. and

SUMMARY

The efficacy of sublingual nifedipine in attenuating the pressor responses to laryngoscopy and intubation was studied in 40 patients undergoing elective surgery. Anaesthesia was induced with thiopentone 5.5 mg kg^{-1} i.v. and tracheal intubation was facilitated with suxamethonium 1.5 mg kg^{-1} i.v. Patients were allocated randomly to receive sublingual nifedipine 10 mg or placebo capsules 10 min before induction. Patients receiving placebo capsule showed significant increases in heart rate and arterial pressure associated with tracheal intubation ($P < 0.001$). The increases in arterial pressure and rate–pressure product were reduced in nifedipine treated patients ($P < 0.001$). Heart rate increased significantly in both groups immediately after intubation.

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$\dot{V}_E$ of approximately 110 ml kg^{-1}. Following recovery from suxamethonium, pancuronium 4 mg was given i.v.

Student's *t* test for paired observations was used for analysis within the groups, and that for unpaired observations for analysis between groups. $P < 0.05$ was considered statistically significant.

RESULTS

There were no significant differences between the two groups in respect of mean age or weight (34.6 ± 3.9 yr, 64.9 ± 4.2 kg in control patients compared with 36.3 ± 3.6 yr, 65.9 ± 5.4 kg in nifedipine treated patients (mean ± SD)). There was no statistically significant difference between the two groups in respect of mean heart rate (HR), systolic arterial pressure (SAP) and mean arterial pressure (MAP) at 0 and 10 min.

SAP and MAP decreased following induction in both groups, but there was no significant difference between the two groups. In response to laryngoscopy and intubation, SAP and MAP increased significantly in control patients ($P < 0.001$), while the increase was significantly less in the nifedipine treated group ($P < 0.01$). The increase in SAP and MAP in group B patients after intubation was 0.9 mm Hg and 3.9 mm Hg, respectively, compared with 20.2 mm Hg and 22.8 mm Hg in control patients (table I).

There was an increase in heart rate after induction, laryngoscopy and intubation in both groups ($P < 0.001$), but no significant difference existed between groups at any stage.

The rate-pressure product (RPP) was significantly higher in control compared with nifedipine treated patients after laryngoscopy and intubation and at 1, 2 and 3 min following intubation ($P < 0.001$) (table I).

The duration of surgery in control (85.5 ± 12.3 min) and nifedipine treated patients (86 ± 10.5 min), and requirements for pancuronium (5.7 ± 0.6 mg and 5.7 ± 0.5 mg, respectively) were comparable.

DISCUSSION

Nifedipine is an antagonist of calcium influx through the slow channel of the cell membrane and has been shown to be an effective treatment for stable, variant and unstable angina and mild to severe hypertension [9–11]. Our study has shown that sublingual nifedipine attenuated the increase in SAP and MAP produced by laryngoscopy and tracheal intubation. Although tachycardia was not

TABLE I. *Mean values (±SD) for cardiovascular variables before nifedipine or placebo (A), pre-induction (B), after thiopentone (C), after suxamethonium D), immediately after intubation (E), and 1, 2 and 3 min following intubation (E+1, E+2 and E+3, respectively) in the two groups. Between-group comparisons, unpaired* t *test*: **P < *0.01*; ***P < *0.001*

	A	B	C	D	E	E+1	E+2	E+3
SAP (mm Hg)								
Control	127.3	127	116.8	129.9	143.7	147.5	141.5	132.8
	±5.5	±5.7	±5.3	±5.6	±6.7	±4.4	±3.7	±4.5
Nifedipine	128.5	126.5	117	123.1**	129.4***	127.4***	121.9***	117.2***
	±7.5	±8.75	±8.6	±6.7	±10.6	±11.9	±10.8	±7.2
MAP (mm Hg)								
Control	98.1	97.6	86.9	105.7	117.3	120.9	112.5	104.8
	±4.1	±4.1	±3.2	±3.8	±5.3	±2.8	±3.2	±2.8
Nifedipine	99.1	96.7	87.7	98.2***	103***	101***	95.4***	92.6***
	±4.6	±5.7	±4.9	±4.5	±5.9	±7.2	±7	±4.1
HR (beat min^{-1})								
Control	73.8	73.7	81	88	94.9	97.2	90.6	84.6
	±3.8	±3.9	±4.3	±5.1	±4.1	±5.4	±4.9	±4.4
Nifedipine	73.1	74.7	81.7	88.5	94.7	97.8	91.3	84.2
	±4.6	±4.9	±5.7	±5.9	±5.8	±6.4	±7	±3.7
RPP								
Control	9395	9360	9496	11438	13644	14339	12817	11238
	±630	±650	±723	±940	±960	±702	±714	±750
Nifedipine	9390	9440	9550	10906	12258***	12478***	11141***	9870***
	±750	±780	±880	±970	±1320	±1650	±1325	±750

obviated, the increase in RPP, an index of myocardial oxygen consumption, was significantly attenuated. The administration of sublingual nifedipine did not produce undue hypotension.

Nifedipine is absorbed well by the oral or sublingual route. After single sublingual administration of nifedipine 10 mg, measurable plasma concentrations were present within 6 min in 50% of volunteers [12]. The onset of an antihypertensive action is obvious within 5–8 min after sublingual administration with peak effects occurring at 20–30 min [13]. The elimination half-life following oral administration varies between 2 and 3.4 h [14].

Sublingual nifedipine has been found to be a safe and effective drug for the acute lowering of increased arterial pressure resulting from surgery [15]. However, calcium antagonists may cause an exaggerated hypotensive response in the presence of volatile anaesthetic agents by either further reducing systemic vascular resistance or reducing myocardial contractility, or a combination of these effects.

In conclusion, we have shown that sublingual nifedipine attenuates the hypertensive response to laryngoscopy and intubation. However, the role of this technique for suppressing pressor responses in the hypertensive patient at the time of tracheal intubation requires further study.

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USE OF DILTIAZEM TO CONTROL CIRCULATORY FLUCTUATIONS DURING RESECTION OF A PHAEOCHROMOCYTOMA

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SUMMARY

This report describes the use of diltiazem to control circulatory fluctuations during anaesthesia in five patients undergoing resection of a phaeochromocytoma. Diltiazem was administered continuously i.v. before anaesthesia and during surgery until the draining vein from the tumour had been ligated. Arterial pressure and systemic vascular resistance decreased in association with the infusion of diltiazem. Heart rate was stable, and there was no ventricular tachyarrhythmia. Arterial pressure was controlled easily during the manipulation of the tumour, and there were no hypotensive episodes after the removal of the tumour.

The anaesthetic management of patients undergoing resection of a phaeochromocytoma has been improved by advances in monitoring [1], and by the introduction of new anaesthetic agents such as enflurane [2, 3] and isoflurane [4, 5]. Preoperative management with the α-blockers, phenoxybenzamine [6] and prazocine [7, 8], has also contributed to the safety of anaesthesia. Even now, however, severe hypertension during the manipulation of the tumour and hypotension after its removal are hazardous and, at times, difficult to control.

Diltiazem, a benzothiazepine derivative, is a calcium channel blocking drug which decreases systemic arterial pressure by inducing arterial vasodilatation. In addition, it has an antiarrhythmic action [9]. It may also interfere with the release of noradrenaline from adrenal medullary tissue [10] and attenuate the increase in arterial pressure in response to exogenous noradrenaline [11].

The purpose of this study was to evaluate the effects of diltiazem on circulatory stability during anaesthesia for the surgical removal of phaeochromocytoma.

PATIENTS AND METHODS

Three male and two female patients (37–66 yr) with a phaeochromocytoma were studied. The procedure was explained in detail and informed consent obtained. The diagnosis of phaeochromocytoma was confirmed by the detection of increased plasma and urinary concentrations of catecholamines. An abdominal computerized axial tomography scan revealed adrenal tumours. Hypertension was paroxysmal in three patients and sustained in two (table I). Phenoxybenzamine was not available in Japan, therefore all of the patients were pretreated with prazocine, labetalol or YM09538 (methylbenzensulphonamide hydrochloride) [12]. Hypertension was well controlled, except in patient No. 5. This patient received prazocine 12 mg and propranolol 30 mg per day although paroxysmal hypertension (systolic arterial pressure greater than 200 mm Hg) occurred at intervals of 1–2 days. The patients were premedicated with diazepam 10–20 mg given by mouth and were well sedated upon arrival at the operating room. The ECG was monitored, and a radial artery was cannulated. A flow-directed pulmonary artery catheter (American Edwards Laboratories) was inserted via the right internal jugular vein. Baseline measurements were made of heart rate (HR), mean arterial pressure (MAP),

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TABLE I. *Preoperative data of five patients. NA = noradrenaline; A = adrenaline; YM09538 = methylbenzensulphonamide hydrochloride. Normal values: plasma NA 0.05–0.40 ng ml*$^{-1}$*; plasma A < 0.01 ng ml*$^{-1}$*; urine NA 10.0–90.0 g day*$^{-1}$*; urine A < 10.0 g day*$^{-1}$

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yr) and sex	66 M	55 M	37 F	47 F	55 M
Hypertension	Sustained	Paroxysmal	Paroxysmal	Paroxysmal	Sustained
Arterial pressure (mm Hg)	150–170/ 80–100	130–170/ 80–110	130–150/ 70–90	140–150/ 70–90	160–170/ 100–110
Heart rate (beat min^{-1})	80–90	70–75	80–85	70–75	70–80
Preoperative medication (mg day^{-1})	Prazocine 3	Labetalol 100 Nifedipine 30	Labetalol 50 Nifedipine 20	YM09538 50	Prazocine 12 Propranolol 30
Plasma NA	0.06	0.46	0.53	0.63	—
Plasma A	0.01	0.23	0.01	0.05	—
Urine NA	201.7	720.4	1327.1	1741.0	3110.0
Urine A	30.7	1285.2	72.2	375.3	25.3

TABLE II. *Haemodynamic data (means ± SD). HR = heart rate (beat min*$^{-1}$*); MAP = mean arterial pressure (mm Hg); PAP = mean pulmonary artery pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); CI = cardiac index (litre min*$^{-1}$ *m*$^{-2}$*); SVR = systemic vascular resistance (dyn s cm*$^{-5}$*).* *P < 0.05, *baseline* v. *diltiazem*

	HR	MAP	PAP	PCWP	CI	SVR
Baseline	75±8	111±12	15±3	10±3	3.41±0.80	1674±304
Before anaesthesia with diltiazem	72±6	96±4*	16±4	8±5	3.32±0.55	1341±315*
After intubation	69±5	74±12	16±4	10±4	2.60±0.39	1311±237
After incision	73±8	84±15	20±4	12±4	2.41±0.40	1561±276
Tumour manipulation	79±8	114±25	23±4	15±4	2.92±0.88	1831±437
Tumour removal	74±13	72±12	15±5	9±4	2.17±0.43	1619±431
After anaesthesia	81±13	106±26	19±3	11±3	2.90±0.95	1626±352

mean pulmonary artery pressure (PAP), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP). Cardiac output was measured using the thermodilution technique. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated using standard formulae.

Diltiazem was administered i.v. at a rate of 3 μg kg^{-1} min^{-1}. The PCWP was maintained at the baseline value by infusion of lactated Ringer's solution. When MAP was greater than 100 mm Hg, or SVR was greater than 1500 dyn s cm^{-5} 30 min after the start of diltiazem, the rate of infusion of diltiazem was increased to 6 μg kg^{-1} min^{-1}. Once the circulation became stable, haemodynamic measurements were performed.

Anaesthesia was induced with 3–5% enflurane and nitrous oxide in oxygen (1:1) during the continuous infusion of diltiazem. Orotracheal intubation was facilitated with vecuronium (patients Nos 1 to 4) or pancuronium (patient No. 5). (Vecuronium is not commercially available in Japan.) Anaesthesia was maintained with 1–3% enflurane and 50% nitrous oxide in oxygen. Ventilation was controlled, and vecuronium or pancuronium given to provide continued neuromuscular blockade. Hypertension during the exploration of the abdomen was controlled by increasing the inspired concentration of enflurane or by increasing the infusion rate of diltiazem to 10 μg kg^{-1} min^{-1}. If systolic arterial pressure remained greater than 200 mm Hg in spite of this treatment, phentolamine was administered. Propranolol was given if a tachyarrhythmia was noted. The infusion of diltiazem was continued until the draining vein from the tumour had been ligated. Hypotension, after removal of the tumour, was treated by the rapid infusion of fluid. At the end of surgery, neuromuscular block was antagonized with neostigmine 1.0 mg (and atropine

TABLE III. *Vasoactive drugs, arterial pressure and fluid balance during anaesthesia*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Propranolol (mg)	0	0	0	4	0
Phentolamine (mg)	0	2	0	22	0
Diltiazem					
Total dose (mg)	30	45	30	40	40
Infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)	3.0–6.0	3.0–4.5	3.0	3.0	5.0–10.0
Peak arterial pressure during tumour manipulation (mm Hg)	122/68	204/114	138/80	222/100	162/84
Lowest arterial pressure after tumour removal (mm Hg)	104/54	96/50	102/52	88/46	90/54
Fluid balance (before/after tumour removal) (ml/ml)					
Crystalloid solution	1200/400	2400/650	2900/550	2800/600	2300/500
Colloid solution	0/0	300/200	0/0	0/0	0/0
Blood transfusion	0/0	0/0	0/0	0/600	600/400
Blood loss	150/150	1100/400	300/200	700/300	1500/900

0.5 mg). The trachea was extubated and the patient transferred to the recovery room.

Haemodynamic measurements were performed before the infusion of diltiazem, during the infusion of diltiazem before anaesthesia, after intubation and before surgical incision, during exploration of the abdomen, during tumour manipulation, after removal of the tumour and once anaesthesia had been terminated.

All data are presented as the mean and standard deviation. Comparisons between baseline values and values during infusion of diltiazem were performed with the paired Student's t test. A P value of less than 0.05 was considered significant.

RESULTS

Haemodynamic data for the duration of the study are presented in table II, and details of observations during anaesthesia in table III.

Heart rate remained stable and was between 69±5 and 79±8 beat min^{-1} during anaesthesia. There was no ventricular tachycardia. Propranolol was used only in patient No. 4, to treat ventricular premature beats.

Average MAP (fig. 1) decreased significantly from 111±12 to 96±4 mm Hg with diltiazem and increased to 114±25 mm Hg during manipulation of the tumour (event 5). Peak systolic arterial pressures were 204 mm Hg, and 222 mm Hg (patients Nos 2 and 4, respectively), although they returned to less than 200 mm Hg within 1 min.

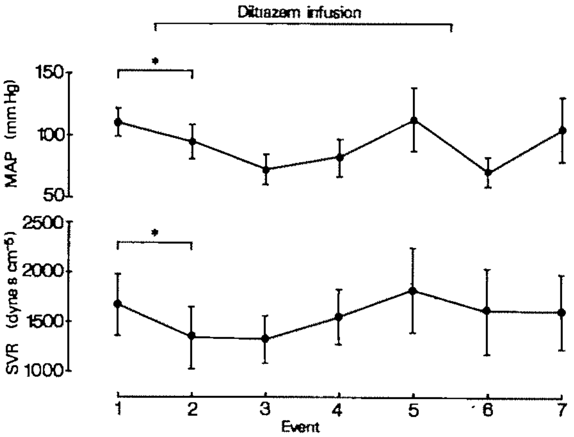

FIG. 1. Changes (mean, SD) in mean arterial pressure (MAP) and systemic vascular resistance (SVR). MAP and SVR decreased significantly after the start of diltiazem infusion. MAP increased to 114 mm Hg during tumour manipulation and decreased to 72 mm Hg after removal of the tumour. MAP was maintained within a relatively narrow range throughout the operation. SVR was less than 1500 dyn s cm^{-5} with diltiazem infusion, but reached 1831 dyn s cm^{-5} during tumour manipulation. Events: 1 = Baseline; 2 = before anaesthesia, with diltiazem; 3 = after intubation; 4 = after surgical incision; 5 = tumour manipulation; 6 = tumour removal; 7 = after anaesthesia. $^{*}P < 0.05$, 1 v. 2.

Total dose of phentolamine was 2 mg in patient No. 2, and 22 mg in patient No. 4. In the other three patients, peak systolic arterial pressure was below 200 mm Hg and phentolamine was not required. Average MAP decreased to 72±12 mm

Hg after removal of the tumour; no vasoconstrictive drugs or inotropic agents were required to treat the decrease in arterial pressure.

PAP and PCWP were stable during the infusion of diltiazem. Both values increased during manipulation of the tumour but returned to their baseline values after the removal of the tumour. Cardiac index did not change when diltiazem was administered initially, but decreased after the induction of anaesthesia with enflurane; it decreased further after the removal of the tumour before returning partially towards baseline once anaesthesia was discontinued.

Mean SVR (fig. 1) decreased significantly from 1674 ± 304 to 1341 ± 315 dyn s cm^{-5} with diltiazem, increased after incision, reached 1831 ± 437 dyn s cm^{-5} during tumour manipulation and decreased after removal of the tumour.

All of the patients had an uneventful postoperative course.

DISCUSSION

The principal finding of this study was that diltiazem effectively minimized the changes in arterial pressure and heart rate. Arterial pressure was easy to control, and heart rate was remarkably stable. There were no serious ventricular premature beats.

The anaesthetic management during the removal of a phaeochromocytoma is sometimes difficult because of the fluctuations in arterial pressure and tachyarrhythmia. Increased secretion of catecholamines by the tumour results in vasoconstriction and a reduction in the circulating blood volume. Preoperative expansion of the plasma volume using an α-blocker is the key to safe anaesthesia. Phenoxybenzamine has been the most useful drug and prazocine is now accepted in clinical use [7, 8]. We evaluated the preoperative haemodynamic state and tried to estimate the degree of vasoconstriction. In spite of the preoperative administration of an α-blocker, SVR was increased. Therefore, we gave diltiazem at a rate of 3–6 $\mu g\ kg^{-1}\ min^{-1}$ to reduce SVR. SVR decreased by 20%, to less than 1500 dyn s cm^{-5} in four of the five patients. This expansion of the plasma volume decreased the cardiovascular changes evident during anaesthesia. Vasodilators given during surgery have also been recommended for the control of arterial pressure. Phentolamine is commonly used for the treatment of hypertensive episodes [3, 13]; however, it results in tachycardia and tachyphylaxis. Sodium nitroprusside [3–5], nitroglycerin [14], prostaglandin E_1 [15] and nicardipine [13] have also been used to control hypertension. However, the clinical efficacy of these drugs has not been systematically evaluated.

Diltiazem is a calcium channel blocker with an antihypertensive effect and an antiarrhythmic action. The hypotensive effect of diltiazem can be attributed not only to direct vasodilatation, but also to attenuation of the pressor effect of the catecholamines [11]. The hypotensive effect of the drug is noticeable within 1 min. When the infusion is stopped, recovery from the effects of diltiazem occurs in a few minutes. This rapid but reversible action is beneficial in the treatment of hypertensive crises.

It has also been demonstrated that the reflex tachycardia usually associated with a decrease in arterial pressure does not develop with diltiazem [9, 16]. In our patients heart rate decreased slightly with diltiazem. This stabilization of heart rate is important because patients with phaeochromocytoma readily become ischaemic, as a result of longstanding hypertension and catecholamine-induced cardiomyopathy [17].

The antiarrhythmic action is another benefit of diltiazem. Although concentrations of the catecholamines were not measured during surgery in our patients, they could, theoretically, have been 10 to 50 times greater than preoperative values [1, 3, 15]. Increases in adrenaline concentration can result in dangerous arrhythmias. However, propranolol was required, in only small doses, in one of the five patients. Many investigators have reported that diltiazem was effective as an antihypertensive or antiarrhythmic agent, although there have been no reports that diltiazem was administered to control the haemodynamics of patients with phaeochromocytoma.

Recently, several investigators reported a relationship between calcium channel blockers and catecholamine secretion from adrenal medullary tissue. Pinto and colleagues [18] reported that the calcium channel blocker methoxyverapamil inhibited the release of catecholamines from the adrenal medulla perfused *in vitro*. Serfas and coworkers [19] demonstrated that another calcium channel blocker, nifedipine, suppressed noradrenaline secretion by a phaeochromocytoma. On the other hand, Lenders and associates [20] and Favre and colleagues [21] reported that nifedipine did not have a direct influence on catecholamine release from the tumour—although it might interfere with the action of catecholamines in patients with phaeochromocytoma. Hypertensive crises during surgery occur when catecholamines are suddenly released from the tumour in response to manipulation. Therefore, the interaction between calcium channel blockers and catecholamines may be beneficial in the treatment of hypertension.

Another problem is severe hypotension which may follow the removal of the tumour. This problem may result from the reduced circulating blood volume consequent upon the intense vasoconstriction and sudden vasodilatation following removal of the tumour and the resultant decrease in catecholamine concentration. Catecholamine-induced cardiomyopathy may induce further deterioration. In our patients, MAP decreased to 72 ± 12 mm Hg after removal of the tumour, but no positive inotropic agents or vasoconstrictive drugs were required. Our findings suggest that diltiazem produced enough vasodilatation to expand the circulating blood volume and attenuate the cardiovascular changes.

No side effects of diltiazem were observed in our study. However, diltiazem has a weak negative inotropic action and inhibitory effects on the atrioventricular node and the sinus node. Therefore, it may have adverse interactions with the β-adrenergic blocker, propranolol. Diltiazem should be given cautiously in the presence of pre-existing β-adrenergic blockade.

In conclusion, the continuous infusion of diltiazem, given before and during anaesthesia, attenuated the cardiovascular changes during surgery and appeared to play a useful role in the control of haemodynamic status in patients with a phaeochromocytoma.

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ANAESTHESIA FOR ISOLATED LUNG TRANSPLANTATION

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SUMMARY

The anaesthetic management of a patient undergoing successful, left-sided orthotopic single lung transplantation is presented. Problems, specific to the operation, are featured and discussed.

The Toronto Transplant Group has obtained consistent success with isolated lung transplantation in selected patients [1, 2]. The recipient operation is conducted in a way similar to pneumonectomy. Facilities for partial cardiopulmonary bypass are available, but are not used unless warranted by untoward intraoperative events that are otherwise difficult to treat. Most of the potential for such events is related to anaesthetic and surgical manoeuvres and their times of onset are predictable.

After 2 years of laboratory animal research into pulmonary preservation, using a model of canine unilateral pulmonary allotransplantation (McGregor, personal communication) and following the successful initiation of heart transplantation in Newcastle, it was decided to undertake a programme of lung transplantation.

CASE REPORT

A 43-year-old female, weighing 56 kg, and diagnosed as suffering from end-stage pulmonary fibrosis as a result of eosinophilic granuloma, was accepted into the programme for isolated, orthotopic lung transplantation. Therapy with steroids and cyclophosphamide had failed to halt the advance of the disease. The patient was breathless on minimal exertion, and required oxygen supplementation at rest. The results of cardiorespiratory assessment are shown in table I. In summary, these demonstrated mild restrictive pulmonary deficit, markedly reduced diffusing capacity, normal left and right ventricular function and increased pulmonary vascular resistance that was unaltered by pulmonary vasodilators. Her prognosis for survival in excess of 1 year was poor. She was started on a conservative regimen and a weight-reducing diet to improve her general health. By the time a suitable donor was found she weighed 50 kg.

Anaesthesia

With the patient under light sedation with fentanyl 25 μg, droperidol 2.5 mg and midazolam

TABLE I. *Preoperative physiological assessment values*

Respiratory			
Forced expiratory volume (FEV_1) (litre)			2.05
Vital capacity (VC) (litre)			2.65
FEV_1/VC (%)			77
Transfer factor (mmol min^{-1} kPa)			0.8
Diffusion constant (mmol min^{-1} kPa $litre^{-1}$)			0.26
Haemodynamic			
Cardiac output (litre min^{-1})			5.0
Cardiac index (litre min^{-1})			3.29
Total peripheral resistance (dyn s cm^{-5})			592
Pulmonary vascular resistance (dyn s cm^{-5})			496
Cardiac pressures (mm Hg)	Systolic	Diastolic	Mean
Right atrium	4	−2	2
Right ventricle	63	6	
Pulmonary artery	58	25	37
"Wedge" pressure	10	2	6
Left ventricle	130	6	
Aorta	130	75	90

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2.5 mg, and puncture site infiltration with lignocaine, a peripheral i.v. and radial arterial cannulae were inserted. A 16-gauge central venous cannula was also inserted via the antecubital fossa and an infusion of equine antithymocyte globulin was started through it. The patient's oxygen saturation was monitored continuously with a pulse oximeter sensing from a transducer attached to her left ear lobe.

Anaesthesia was induced with a bolus of alfentanil 1 mg, fentanyl 50 µg, followed by etomidate 10 mg and vecuronium 10 mg. A size 37-gauge right-sided double-lumen tube was inserted to the trachea and right main bronchus. Both lungs were ventilated with 50% oxygen and 0.5% enflurane in air. A triple-lumen catheter was placed in the right internal jugular vein and a sheathed thermodilution catheter placed in the left internal jugular vein with the tip sited in the main pulmonary artery.

A Servo Elema 900A ventilator was used with the ventilatory rate set to maintain the peak inflation pressure at approximately 20 cm H_2O, and the minute volume adjusted to maintain normocapnia. A fractional inspired concentration of oxygen ($F\text{I}_{O_2}$) of 0.5 maintained cutaneous oxygen saturation in excess of 90% when both lungs were being ventilated. An infusion of dopamine 3 µg kg^{-1} min was started through one limb of the triple-lumen catheter, sodium nitroprusside 3 µg kg^{-1} min through the second, and the third was utilized for monitoring central venous pressure. These latter drugs were used empirically: the dopamine for its effect on renal function, and the sodium nitroprusside to counteract pulmonary vasoconstrictive responses to anaesthesia or surgery.

An upper midline laparotomy was performed to mobilize omentum, which was delivered into the chest ready for wrapping around the bronchial anastomosis. While this procedure progressed the left limb of the double-lumen tube was clamped and the effects of one-lung anaesthesia assessed. Oxygen saturation remained unchanged and no untoward events occurred, therefore one-lung anaesthesia was continued for the rest of the procedure, the repositioning for thoracotomy, and the left pneumonectomy. The left lateral thoracotomy position was utilized for the pneumonectomy, and the left groin was prepared for surgery in case access to the femoral vessels for partial cardiopulmonary bypass proved necessary. Before pneumonectomy the left pulmonary artery was test clamped. This produced a steep increase in pulmonary artery pressures, which were maintained despite an increase in infusion of nitroprusside to 6 µg kg^{-1} min. No other significant respiratory or haemodynamic events occurred at this juncture, therefore left pneumonectomy was carried out. Anaesthesia was maintained with enflurane in air with $F\text{I}_{O_2} = 0.5$. Fentanyl and vecuronium were administered, as judged necessary, to total doses of 900 µg and 30 mg, respectively, for the 4.5 h of anaesthesia.

Soon after the thorax was opened it was noted that the thermodilution catheter lay in the left-sided superior vena cava. Because the tip was correctly sited, this did not give rise to problems of pressure measurement, but the anatomical anomaly restricted surgical access to the recipient's left atrium. The anastomosing of the donor pulmonary veins to the recipient left atrium and the donor pulmonary artery to that of the recipient proved awkward and it was felt essential that vascular junctions should be assessed before the bronchial anastomosis was embarked upon. When the vascular clamps were released a dramatic reduction in pulmonary artery pressure occurred, the donor lung was perfused preferentially and a large shunt occurred with oxygen saturations declining rapidly to 40%. A 7.5-mm cuffed tracheal tube was placed in the donor bronchus by the surgeon. This was ventilated periodically by the anaesthetist with manual pressure on a reservoir bag, attached to a separate oxygen supply, and connected to sterile plastic tubing that crossed into the surgical field to a catheter mount on the tracheal tube. In this way oxygen saturations could be increased as necessary during the critical phase as the bronchial anastomosis was being fashioned around the tracheal tube sited in the donor bronchus. Normal ventilation, through the left side of the double-lumen tube, was reinstituted on completion of this anastomosis.

Total operative blood loss, estimated from swab weighing and measurement of suction loss, was 200–300 ml. Intraoperative fluid replacement was restricted to 100 ml of crystalloid in the form of dextrose saline solution, and 400 ml of colloid as hetastarch.

At the end of the operation, a nasogastric tube and a urinary catheter were inserted and the double-lumen tube exchanged for an 8.5-mm orotracheal tube with a "Hi–Lo" cuff, before transfer to the intensive care unit for elective postoperative ventilation. Ventilation settings were similar to those used during anaesthesia, 5 cm H_2O positive end-expiratory pressure was added and $F_{I_{O_2}}$ set at 0.5 in air. Dopamine and nitroprusside were continued in doses of 5 and 5 $\mu g\ kg^{-1}$ min, respectively.

Twelve hours later clinical evidence suggested that ventilatory assistance was no longer necessary. The patient's trachea was extubated after spontaneous ventilation had been re-established satisfactorily with 30% oxygen in air. Dopamine and vasodilator treatment were continued for a further 24 h. Fluid replacement was maintained strictly as low as that consistent with an adequate renal output with central venous pressure maintained at less than 6 cm H_2O and i.v. infusion at 1 ml kg^{-1} h.

There were no further serious respiratory problems. On the 14th day after operation the patient developed a fever and a small pleural effusion, and the fever recurred on the 16th and 21st days after operation. These three events, almost certainly indicative of rejection, responded to short courses of high-dose steroid therapy. Oxygen saturation ($F_{I_{O_2}} = 0.21$) stayed in excess of 85% throughout the recovery period. The patient was discharged from the intensive therapy unit on day 3 after operation and from hospital, free of the need for supplementary oxygen, on the 35th day after operation.

DISCUSSION

Patients submitted for isolated lung transplantation are at most danger at three stages during the procedure. First as one-lung anaesthesia is commenced, second when the pulmonary artery of the lung to be excised is clamped, and third when the donor lung is perfused but not ventilated (DeMajo, personal communication). Abnormalities in recorded variables, shown in table II, occurred at each of these points in this patient.

Despite increasing minute ventilation at the onset of one-lung anaesthesia, the arterial partial pressure of carbon dioxide remained increased. This may have been a result of an inadequate number of alveoli for ventilation in the lung being used for anaesthesia. In the event it reached a plateau and no complications from this cause ensued.

TABLE II. *Intraoperative variables. Events: 1 = Patient awake, spontaneous ventilation; 2 = two-lung positive pressure ventilation, laparotomy; 3 = one-lung ventilation, thoractomy, pulmonary artery test clamped; 4 = recipient pneumonectomy completed; 5 = donor lung perfused but not ventilated; 6 = operation completed, two-lung positive pressure ventilation*

	Systemic AP (mm Hg)			Pulmonary AP (mm Hg)						
Event	S	D	M	S	D	M	CVP (mm Hg)	$F_{I_{O_2}}$	P_{O_2} (kPa)	P_{CO_2} (kPa)
1	98	56					8	0.4	12.4	5.3
2	100	60	80	53	25	37		0.5	25.8	7.5
3	110	60	82	81	31	51		0.5	14.3	7.20
4	95	57	69	67	33	50	14	0.5	9.1	8.0
5	85	70	77	42	34	25	19	1.0	6.2	9.63
6	90	57	73	39	18	28	8	0.6	13.6	5.57

Recorded pulmonary artery pressures at the time of clamping of the left vessel became grossly increased, reaching two-thirds of systemic values with a mean in excess of 50% of the mean systemic pressure throughout this phase of the operation. There is normally a significant increase at this stage of a pneumonectomy, but values as high as these have not been reported [3]. The patient appeared not to suffer any deleterious effects. Efforts were made to reduce pulmonary artery pressure with sodium nitroprusside, but as the right ventricle continued to function well and there was no increase in right atrial pressure, this was not increased further.

It has already been realized that the key preoperative assessment before submission for lung transplantation by this method is that of right ventricular function. This patient had no detectable preoperative deficit and appears to have withstood the artificially induced sudden increase in pulmonary vascular resistance without detectable evidence of decompensation. Normally, left pneumonectomy is the operation of choice as it is technically easier [4], but the presence of a left-sided superior vena cava in this patient led to an operative event that proved to be the most serious. Because of this, the sequence of surgery reverted to that used in earlier reported cases. Severe oxygen desaturation as a result of perfusion of the replacement lung before its ventilation leads to increased physiological shunting. Reclamping of the pulmonary artery, its partial clamping, or ventilation of the donor lung by a second system such a high frequency jet ventilation through a narrow-bore tube that traverses the transected main bronchus reduces the severity of the degree of desaturation (DeMajo, personal communication). Recommendations for the operative technique have now been altered so that, if possible and in those with normal anatomy, all anastomoses, vascular and bronchial, with the donor lung are completed before its full perfusion and ventilation are commenced.

As experience in the operation of isolated lung transplantation is still limited, some aspects of the conduct of anaesthesia in this patient were based on theoretical considerations; others were to some extent empirical. The use of air as carrier gas is known to reduce alveolar collapse because of the splinting effect of nitrogen, and avoids precipitating the shunt effects of ventilation with 100% oxygen [5]. Nitrous oxide was avoided because it has been shown to increase pulmonary vascular resistance [6]. The use of a volatile agent, in low doses, was not avoided as the disadvantages in such surgery may be more theoretical than practical [7].

Dopamine was used throughout the operation and into the postoperative period, but only in small, "renal", doses. This was for two reasons. The major problem of reimplantation is the inability of a transplant lung to handle excess fluid loads. Fluid restriction after operation and the maintenance of a good urine output are necessary. Polson and colleagues [8] have recently demonstrated the value of dopamine prophylaxis in orthotopic liver grafting. Following both lung and liver transplants, patients receive nephrotoxic drugs, such as Cyclosporin A, as part of their immunotherapy and it would seem logical, therefore, to ensure that the kidneys function optimally at a time of active fluid restriction.

The role of pulmonary vasoactive drugs remains to be elucidated. Workers in Toronto, Canada—the only centre in the world to report consistent success with this operation—use sodium nitroprusside (DeMajo, personal communication). Others, in the field of heart–lung transplantation, have reported the use of aminophylline [9]. Although it had been shown before operation in our patient that the increase in pulmonary vascular resistance was not reduced following administration of sodium nitroprusside, this drug was used empirically to reduce any undefined effects that anaesthesia or surgery may have had on pulmonary haemodynamics or systemic vascular resistance.

The patient is presently healthy and is living a normal life 6 months after the operation. Clearly, further experience is necessary to define the validity of the anaesthetic technique used for this operation.

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APNOEA ASSOCIATED WITH THE INTRATHECAL ADMINISTRATION OF MORPHINE IN OBSTETRICS

A Case Report

E. ABOULEISH

SUMMARY

The intrathecal administration of hyperbaric morphine 1 mg for pain relief during labour was followed, 7 h after injection, and 1 h after delivery, by respiratory depression. Pulse-oximetry was helpful in alerting the medical personnel. After an initial 1 mg of naloxone i.v. in increments of 0.1–0.2 mg, a continuous infusion of naloxone 0.4 mg h^{-1} i.v. was used to prevent a recurrence of the respiratory depression. The total dose of naloxone over an 8-h period was 3.6 mg.

Respiratory depression has been described in association with the intrathecal administration of morphine for the control of postoperative pain [1–11]. In obstetrics, on the other hand, intrathecal morphine 0.5–2 mg has been used successfully without evidence of respiratory depression [12–16]. Nevertheless, the potential for respiratory depression always exists and makes the routine use of the technique in obstetrics difficult to accept [17]. This report describes the occurrence of respiratory depression in a parturient in association with the administration of morphine by the intrathecal route.

CASE REPORT

A 21-year-old primiparous woman (weight 61 kg, height 160 cm) was admitted to the hospital in labour at 38 weeks gestation. At 0800 h, she requested pain relief. The patient's consent was obtained for her inclusion in a study designed to identify the dose–response characteristics of intrathecal morphine in obstetrics. In the Labour Room, with the patient in the left lateral, 30°-reversed Trendelenburg position, lumbar puncture was performed at L3–4 using a 26-gauge spinal needle, and clear CSF was obtained. Preservative-free morphine sulphate 1 mg ml^{-1} (Duramorph) was mixed with 10% dextrose 1 ml to obtain a hyperbaric solution, and the mixture was injected intrathecally at 0820 h. The patient was then turned to the supine position with a wedge under her right hip and maintained head-up in this position. As a part of the design of the study, pain relief was evaluated every 10 min using a visual analogue pain score where 10 represented maximum pain and zero indicated no pain. Heart rate, arterial pressure (Dinamap), degree of alertness, ventilatory rate, and arterial oxygen saturation (Sa_{O_2}) (Ohmeda Biox 3700 with the alarm set at 90% saturation—corresponding to Pa_{O_2} of approximately 65 mm Hg) [18] were recorded at set time intervals. Recordings were obtained every 10 min for 1 h, every 15 min for 2 h, every 30 min for 6 h, then every 1 h for the remaining 24 h. At these time intervals, any side effects such as nausea, vomiting, itching and respiratory depression (defined as a ventilatory rate less than 10 b.p.m. or Sa_{O_2} less than 90%) were noted.

The vital signs during the control period before the intrathecal injection of the morphine were normal and the patient was alert. Following the intrathecal injection of the morphine, the vital signs remained stable, with the exception of drowsiness between the contractions. Partial analgesia started 30 min after the intrathecal injection, but the pain score was never less than 7. The

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analgesia was considered inadequate by the patient, the nurse, the obstetrician and the anaesthetist. Accordingly, at 1023 h extradural analgesia was administered at L3–4 using 0.5% bupivacaine 8 ml. The pain score was 0 10 min after the extradural block. No significant change in the vital signs occurred, although the patient remained drowsy. At 1400 h, the first stage ended with the patient relatively comfortable (pain score 5). At 1450 h, spontaneous delivery of a 3820-g male infant, with Apgar scores of 9 and 9 at 1 min and 5 min, respectively, occurred. Umbilical blood-gas tensions were normal. Local infiltration of the perineum was used for a small episiotomy and its repair. At 1530 h, the patient was transferred to the Recovery Room.

At 1535 h, vomiting was disturbing to the patient and was treated by three increments of naloxone 0.1 mg i.v. at 5-min intervals. Between the episodes of vomiting the patient was sound asleep. Despite the administration of naloxone, Sa_{O_2} decreased to 92%. At 1645 h, a fourth dose of naloxone 0.1 mg was injected i.v. Despite this, and our presence around her, the patient had episodes of unconsciousness with apnoea triggering the pulse-oximeter alarm. When the patient was shaken, she would wake up and breathe; when left alone, she would almost instantaneously lose consciousness and stop breathing. Oxygen was administered by face mask and naloxone 0.6 mg was injected in increments of 0.2 mg over a few minutes. The patient's level of conciousness and ventilatory rate improved. The ventilatory rate stabilized at 20 b.p.m. and Sa_{O_2} at 96%. At 1700 h, a continuous infusion of naloxone was started at 0.4 mg h^{-1} to avoid any recurrence of the episodes of respiratory depression. The infusion was terminated at 2330 h. The total dose of naloxone administered was 3.6 mg in an 8-h period. Subsequently, the postpartum course was uneventful.

DISCUSSION

Respiratory depression following the intrathecal administration of morphine is believed to result from the cephalad migration of the drug within the cerebrospinal fluid (CSF) and the subsequent depression of the respiratory centres on the floor of the fourth ventricle [19]. The CSF from the lumbar region ascends to reach the cisterna magna in 1–2 h then passes through the foramina of Luschka and Magendie to the fourth ventricle in 4–8 [20]. Intrathecal morphine, by following this pathway, is maximally concentrated in the medulla oblongata 6 h after intrathecal injection [21]. The slow cephalad migration of morphine plus its slow clearance [19] explain the occurrence of late respiratory depression.

Respiratory depression does not occur in every patient receiving intrathecal morphine. The predisposing factors include the intrathecal injection of a large dose of morphine (5-20 mg) [3–5]; advanced age [3–5, 8]; the concomitant administration of central nervous system depressants [3, 5]; the concomitant administration of local anaesthetic [1, 2, 5]; reduced ventilatory capacity [3, 9]; and horizontal or Trendelenburg position [8]. Usually, more than one factor exists. Patients with chronic pain are less susceptible to respiratory depression as a result of the development of tolerance to opioids [22].

Naloxone has been used to prevent and treat the side effects of intrathecal morphine [1, 2, 4, 5, 16]. In the treatment of respiratory depression, the author recommends a continuous infusion of naloxone i.v. after an initial loading dose, since the respiratory depression produced by intrathecal morphine may last longer than the effects of a single dose of naloxone. As a prophylactic measure, the continuous infusion of naloxone has its merits [16], but the use of intrathecal morphine then becomes complicated and costly because of the need for continuous monitoring and continuous infusion, at a time when the mother needs some privacy and rest.

In this report, the time interval from the injection of morphine to the respiratory arrest was 7 h, and coincided with the time course of the slow rostral spread of the drug. The absence of pain from the contractions and the quietness of the Recovery Room may have contributed to the depression of the central nervous system.

In this patient, apnoea occurred *gradually*, with a gradual decrease in Sa_{O_2} which was accompanied by marked drowsiness. Respiratory depression was a manifestation of generalized CNS depression. The pulse-oximeter was helpful in monitoring this patient and correlated well with the observed respiratory depression.

Based on previous studies [12, 13, 15, 16], the young age of pregnant women, and the hyperstimulation of the respiratory centres during pregnancy [23], many anaesthetists thought that life-threatening respiratory depression would not follow the intrathecal administration of morphine provided that the dose did not exceed 1 mg, no CNS depressant was being administered concomitantly, and there was no respiratory disease. This report shows that we were wrong. Therefore, until a dose–response study is done to estimate the minimal effective dose of intrathecal morphine in obstetrics, or an opioid is discovered which acts only on receptors mediating analgesia, with no effect on the receptors mediating respiration, the author feels that intrathecal morphine should be administered only in those situations in which close supervision is possible and in which resuscitation facilities are immediately available.

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CORRESPONDENCE

INTRATHECAL OR EXTRADURAL WHICH APPROACH FOR SURGERY?

Sir,—It was nice to read the editorial in the April 1987 issue of *British Journal of Anaesthesia* [1]. I would like to go one step further and to extend the views on the topic of vertebral regional blocks.

We have been using both for many years and we have developed a philosophy such that extradurals are for young people and the intrathecal route for the old, with few exceptions. One of these is emergencies in obstetrics, where hypovolaemia is not a factor. There, an intrathecal block is a simple and safe way to give good anaesthesia without any loss of time. The reason for this distinction in age is the incidence of postspinal headaches in young people, which ranges between 2 and 8%, no matter which gauge of needle is used [2]. Old people, on the other hand, are not affected with these kind of headaches or, if they are, experience mild forms very rarely.

It is based on this fact that we indicate extradural block and intrathecal block according to the age of the patient, the urgency of the procedure and the acceptance of the individual for a regional technique. If it is going to be a long operation, we use continuous techniques. So far, we have managed more than 600 cases of continuous intrathecal blockade in geriatric patients, mainly for poor risk cases. The results have been outstanding [3–5].

To improve on this we always provide some form of light general anaesthesia for our patients, mostly with nitrous oxide–oxygen, with or without tracheal intubation. If it is necessary, we sometimes reinforce this mixture by low concentrations (0.25 or 0.5%) of enflurane, halothane or with the repeated addition of i.v. agents in very small doses (fentanyl 10–20 µg, flunitrazepam 200 µg) to guarantee comfort and unconsciousness. The tracheal tube allows safe control of the airway. This is always an important detail for upper abdominal operations where traction and incomplete blockade of the sympathetic and the phrenic nerve give rise to reflex responses. The fact that the vagi are not interrupted contributes to these difficulties.

We gave the combination of general anaesthesia and regional blockade the name "Narcoanalgesia". With it we get the best of both worlds: sleep from the inhalation agents and freedom from pain by the blockade of afferent fibres. The paralysis of the motor nerves gives an extra bonus by making the use of neuromuscular blocking drugs unnecessary.

For our daily routine we still use tubocurarine when we wish to control ventilation. Small amounts are used and there is never the need to give neostigmine or any other similar antagonist at the end of this intervention.

With or without supplementation, intrathecal block as a single or continuous technique is the ideal for the older age group, for all kinds of procedures below T6. For upper abdominal surgery, narcoanalgesia is, of course, essential, with tracheal tube in place; 18-gauge extradural Tuohy needles and 20-gauge nylon catheters are well suited for this technique. The agent of choice is 2% lignocaine. This is prepared from a 5% hyperbaric glucose solution (100 mg in 2 ml) diluted with CSF to obtain a final concentration of 20 mg ml^{-1}. Effective anaesthesia–analgesia for 45–60 min is obtained with 20–30 mg, and the dose is repeated as many times as it is needed. The patient's requirement is titrated quite easily and the response to each injection takes about 30 s.

Besides the safety and facility of use of this method, there is the additional attraction of low cost—a very important consideration in much of the world.

There are no "total spinals" or toxic reactions from the local anaesthetic agent with this technique.

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Sir,—I would like to comment on the editorial by Dr Wildsmith on the extradural *v.* intrathecal anaesthesia debate [1]. In our practice, we perform approximately 100 orthopaedic outpatient procedures on the lower extremities per month. The majority are in healthy adults who have been injured in sporting events; many are requiring arthroscopy of the knee. Until 18 months ago, regional anaesthesia had been exclusively intrathecal, and we had one or two patients per month requiring extradural blood patches for lumbar puncture headache.

Over the past 18 months, we have increasingly used extradural anaesthesia and have noted a marked reduction in the incidence of lumbar puncture headache. Dr Wildsmith raises the interesting question of the time taken to establish extradural or intrathecal blockade; for intrathecal block we place a needle in the operating room, but for extradural block we place the catheter whilst the patient is in the holding area. We started using lignocaine for extradural blockade, but now use 2% mepivacaine with 1 ml of bicarbonate added for every 10 ml of mepivacaine [2]. We have found this carbonated mepivacaine to be very effective, with a rapid onset (between

5 and 15 min) and adequate duration for the outpatient orthopaedic proceedures that we are undertaking. We have also administered carbonated mepivacaine with adrenaline which has been adequate for 2 h or more of surgery before a further dose. We have noted that, using extradural blockade, tourniquet pain appears to be less of a problem than in patients who have intrathecal block. In addition, a percentage of patients having intrathecal blockade have delayed discharge from the outpatient unit as a result of difficulty in urination, whereas this appears to be less of a problem with extradural blocks.

In summary, we have evolved a regimen of using extradural block for individuals who are younger than 40 years or so, and reserve subarachnoid block for subjects in the middle and later years of life, when the incidence of spinal headache is much lower [3] and the technical difficulty of obtaining satisfactory extradural block is greater. We feel that 2 % mepivacaine is an ideal agent for extradural use and one which has a very rapid onset when used with bicarbonate, and a low rate of complications. In addition, the extradural route has a greater degree of acceptability with some patients as there appears to be a considerable number of individuals who feel reassured that they are not having a 'spinal' anaesthetic!

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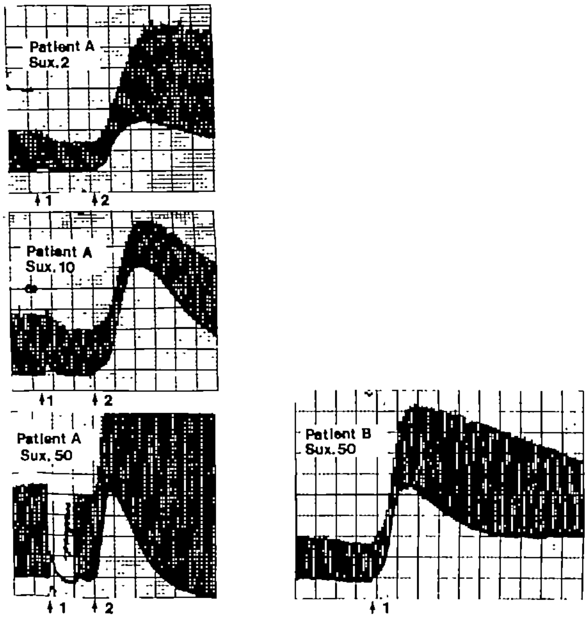

FIG. 1. Suxamethonium (Sux.)-induced *in vitro* contracture of MHS human skeletal muscle. In patient A, three different muscle fascicles were exposed to suxamethonium 2, 10 and 50 mmol litre^{-1} at arrows indicated by 1 under each panel. After the suxamethonium contracture, 3 % halothane was bubbled through the muscle bath, and contracture occurred in each fasicle. Patient B, brother of patient A, had a contracture response to suxamethonium 50 mmol litre^{-1} alone that was relatively large and not totally reversed. Two other fascicles from patient B responded similarly to addition of suxamethonium 50 mmol litre^{-1}.

SUXAMETHONIUM AND MHS MUSCLE

Sir,—Results of an interesting study from Dr Denborough's laboratory [1] produced a conclusion that pure suxamethonium chloride does not induce *in vitro* contracture of muscle from malignant hyperthermia susceptible (MHS) pigs. In a most convincing way, the study provided evidence to show that concentrations of preservatives contained in commercial preparations of suxamethonium were capable of producing the contracture effects previously ascribed to suxamethonium applied to human [2] and pig [3] MHS muscle.

Our laboratory is an MH diagnostic and research unit with considerable experience with *in vitro* contracture testing of human (> 250) and pig (> 200) skeletal muscle. Recently, we have re-initiated studies on the use of suxamethonium for *in vitro* diagnostic contracture testing for MHS. Among five MHS human patients with phenotype H [4] diagnosis, two had muscle that produced contracture responses to *in vitro* application of suxamethonium 50 mmol litre^{-1} or less, prepared from crystalline material purchased from Sigma Chemical, U.S.A. (fig. 1). These two patients (A and B, figure 1) are brothers and their mother's muscle, also phenotype H, was not exposed to suxamethonium 50 mmol litre^{-1}, but did have 0.25-g contracture when exposed to suxamethonium 5 mmol litre^{-1}. The other three MH patients are not related. Gracilis muscle biopsied from four MHS, phenotype H pigs also had *in vitro* contracture response to suxamethonium 50 mmol litre^{-1} and a typical response is illustrated in figure 2. The contracture responses observed in pigs differed from those in MHS human muscle in that two phases occurred (fig. 2). Immediately after application of suxamethonium, the MHS pig muscle produced a contracture with rapid onset and relatively fast reversal. This contracture phase was then followed by a second contracture with slower onset and without reversal during the observed time before halothane was added (fig. 2). It is tempting to speculate that the initial contracture is related to the primary depolarizing effect of suxamethonium, and the second contracture is produced by some other suxamethonium effect. Galloway and Denborough [1] state that motor end-plates do not exist in bundles of muscle fibres and quote a reference [5] that does not support such a notion. Even though these *in vitro* muscle preparations are directly stimulated, it is possible that some indirect nerve stimulation can be contributory, albeit only to a small percentage. It is possible, as suggested by the authors, that *in vivo*, the muscle activating effect of suxamethonium during depolarization could initiate events producing the abnormal release of Ca^{2+} in MHS muscle. A similar mechanism could be occurring *in vitro* or suxamethonium could have a secondary

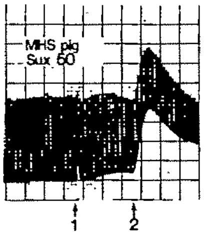

FIG. 2. Suxamethonium (Sux.)-induced *in vitro* contracture of MHS pig skeletal muscle. At arrow 1, suxamethonium 50 mmol litre^{-1} produced a small contracture that was rapidly reversed, and a slower tonic contracture followed. At arrow 2, addition of 3% halothane produced an additional large contracture.

effect on skeletal muscle that contributes to the abnormal response in MHS muscle. Further studies are needed to clarify these effects of suxamethonium on MHS muscle. The impact of genetic influences should also be considered, as not all MHS muscle treated *in vitro* responds abnormally to suxamethonium. It may also be that the MH susceptibility of the animals used in Galloway and Denborough's study differed from those used by us. Finally, the 50-mmol litre^{-1} concentration of suxamethonium used in this study is far in excess of clinical concentrations. Therefore, we do not know if the contractures observed are relevant to actions of the drug under clinical usage. However, halothane, which potentiates the contracture effects of suxamethonium *in vitro*, or some other potent inhalation anaesthetic probably augments the *in vivo* effects of suxamethonium, since the agents are usually present together in clinical usage.

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LIFE-THREATENING REACTION TO ATRACURIUM

Sir,—In medicine it is perhaps unwise always to accept advice appearing in the journals. The June 1987 edition of the *British Journal of Anaesthesia* contained the following statements: "modification in anaesthetic technique based on a history of allergy, atopy or asthma is unlikely to reduce the likelihood of severe clinical anaphylaxis" [1]; and "provided due care is taken to avoid mixing of drugs, atracurium may be used in patients with a history of asthma or allergic reactions" [2].

I wish to report a severe reaction to atracurium in a patient with a history of asthma and atopy.

A 21-year-old, 60-kg female was admitted with a 2-week history of lower abdominal pain and vaginal bleeding. An ultrasound examination suggested a possible ectopic pregnancy. There was no clinical suggestion of intra-abdominal bleeding. The patient gave a history of eczema and asthma from the age of 14 yr and used a salbutamol inhaler on an infrequent basis to treat acute attacks of bronchospasm. She had never been admitted to hospital with this condition. She had received general anaesthesia on two previous occasions, the first 9 years earlier for appendicectomy. On that occasion the following agents were used: thiopentone, alcuronium, morphine, nitrous oxide, halothane, neostigmine and atropine. The anaesthetic was uneventful. The second occasion was 2 years previously for a minor gynaecological procedure. She received thiopentone, nitrous oxide and halothane without recorded incident.

On examination on the present admission, the patient was in good general health: heart rate 70 beat min^{-1}, arterial pressure 120/60 mg Hg. Auscultation revealed normal breath sounds with no wheeze, even on forced expiration. She had last used her inhaler 3 days before this admission. Chest radiograph was normal. Premedication was diazepam 10 mg by mouth 1 h before coming to theatre. At that time the patient had been fasted for 8 h. She came to the anaesthetic room in a relaxed state. A 19-gauge cannula (Wallace Y-can) was inserted to a vein on the dorsum of the hand. Fentanyl 120 µg with droperidol 1 mg were injected and flushed through with saline. The lungs were preoxygenated for 3 min following this, with no apparent problem.

At this time arterial pressure was 130/70 mm Hg, heart rate 75 beat min^{-1}. Atracurium 35 mg was given over approximately a 10-s period. During this injection the patient coughed several times with a distinctive "barking cough". (Sale [3], Thompson [4] and Bowie [5] all noted this type of cough in patients who subsequently developed anaphylactoid reactions.) On completion of the injection of atracurium, propofol 150 mg was given through the same cannula. Ninety seconds after the administration of atracurium, laryngoscopy was performed and, in line with previous experience with this sequence of neuromuscular blocker–propofol, the vocal cords were widely abducted and intubation with an 8.5 Clearway tracheal tube did not provoke any coughing or movement.

Attempted ventilation using a Mapleson A breathing system revealed severe bronchospasm. There was no possibility of tube obstruction. Systolic arterial pressure had decreased to 50 mm Hg, the ECG trace showed heart rate 90 beat min^{-1}, sinus rhythm. Within 1 min, despite attempted hand ventilation with 100% oxygen, the patient had become cyanosed and her arterial pressure was unrecordable, with no palpable carotid pulses, although ECG showed a rate of 40 beat min^{-1}. A working diagnosis of anaphylactic–anaphylactoid reaction was made and 6 ml of adrenaline 1:10000 was injected down the tracheal tube. At the same time as an internal jugular central line was inserted, hydrocortisone 400 mg and aminophylline 250 mg were given via the peripheral cannula through which Haemaccel was given under pressure. A further 4 ml of adrenaline 1:10000 was given via the central line in view of the lack of initial response to the above therapy. Attempted ventilation with 100% oxygen was continued throughout.

A carotid pulse became palpable 4 min later, after 2000 ml of Haemaccel had been given (central venous pressure had increased from zero to 5 cm H_2O). The ECG monitor showed sinus rhythm 90–100 beat min^{-1} with ST segment depression. It was becoming easier to ventilate the lungs at this time.

Chlorpheniramine 10 mg i.v. was given over a 5-min period, and 0.5% halothane introduced to reduce the risk of awareness and to aid relief of bronchospasm. There was a gradual improvement in the patient's condition over the next 30 min. Arterial pressure increased to 100/40 mm Hg, heart rate 80 beat min^{-1}. A total of 3500 ml of Haemaccel was required to maintain a central venous pressure of 4–5 cm H_2O.

Anaesthesia was continued to allow laparoscopy to be undertaken using 0.5% halothane in nitrous oxide–oxygen and IPPV. Vecuronium 4 mg was given to maintain neuromuscular blockade during the procedure, with no adverse effect.

Laparoscopy revealed only a corpus luteum cyst requiring no active treatment.

Following antagonism of neuromuscular blockade with neostigmine 2.5 mg (preceded by atropine 0.6 mg) the patient made an uneventful recovery with no neurological deficit. Overnight, two further doses of hydrocortisone 200 mg 6-hourly were given. The following day the patient was asymptomatic except for complaining that her face and fingers were swollen. There was generalized moderate oedema, but no evidence of bronchospasm.

During the incident and subsequently, blood was sampled and forwarded to the National Adverse Anaesthetic Reactions Advisory Service at the Royal Hallamshire Hospital, Sheffield (Dr J. Watkins) for immunological screening. The results were rather surprising, considering the severe nature of the reaction. Immunoglobulins IgG, IgA, IgM, IgE and complements C3, C4 and C1 inhibitor proved to be normal in concentration and not involved in the reaction mechanism, the concentrations being similar in all specimens after correction for plasma dilution. Despite the patient's history of atopy, her plasma IgE was normal at 50–60 units ml^{-1} and antibodies to the common allergens—house dust mite and grass pollens—were not detected. The conclusion reached by NAARAS was that there was no evidence to suggest an immune reaction or any other mechanism, except that the patient obviously has a tendency to pulmonary histamine release and having "sensitive cells", rather than specific allergy. It was suggested that, in future, anaesthetic management of this patient should avoid papaveretum, morphine, droperidol, tubocurarine, suxamethonium and alcuronium and a technique of fentanyl–etomidate–pancuronium may be considered.

The severity of this reaction may well have been compounded by the administration of an induction agent known to produce a decrease in arterial pressure secondary to a reduction in systemic vascular resistance, but there have been no reported cases of cardiovascular collapse following the administration of propofol and it has been shown by Fahmy and co-workers [6] not to release histamine, and so may well be thought to be a suitable alternative to thiopentone in asthmatic patients.

Following this incident it is now the practice of this author to avoid the use of atracurium in any patient with a history of atopy or asthma. Such a history may indicate merely an increased sensitivity to histamine rather than a specific immune system-mediated process and suggest that the use of agents with the potential for histamine release be avoided. A case may be made for considering histamine-receptor blockade as part of the preoperative preparation of such patients, although as Thornton [7] points out this is no guarantee that problems will not occur.

The single most important feature of this case report is that, once an anaphylactic–anaphylactoid reaction of such severity as to render the patient without a pulse occurs, the administration of adrenaline, either via the tracheal tube or i.v., must not be delayed.

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Sir—Thank you for the opportunity to reply to the letter of Dr Stirton-Hopkins. The case described appears to be an anaphylactoid reaction to atracurium, fentanyl, droperidol or propofol, with no evidence to suggest one drug in particular being responsible, although experience would suggest atracurium is the most likely. The lack of change in immunoglobulin concentrations cited in support of direct histamine release is of course meaningless, as are most measured blood concentrations in a situation where plasma is lost and 2 litre of Haemaccel infused. The approach taken in most countries with such a patient would be to test the patient intradermally to determine the drug responsible and the safety of other neuromuscular blocking drugs. Dr Stirton-Hopkins's report does not invalidate the hypothesis in our study of the predictive value of an atopic history in selecting patients at risk from anaphylactoid reactions [1], for the reasons outlined in the paper, and for three others:

(1) There is no evidence that severe anaphylactoid reactions can be produced by direct histamine release as a result of drugs given in normal dosage.

(2) There is no evidence that direct histamine release caused by drugs produces severe bronchospasm. Indeed, in the majority of studies associating histamine concentration and clinical features there is no link whatsoever between histamine concentration and bronchospasm [2–4].

(3) Of the eight severe anaphylactoid reactions to atracurium [5–11] so far reported in the literature, Dr Stirton-Hopkins's patient is the second with a history of asthma. Two additional unreported patients in our series have no such history.

While patients with a history of asthma will invariably exhibit bronchospasm as part of an anaphylactoid response, such a history is not a reliable predictor of anaphylaxis to atracurium or any other anaesthetic drug.

M. Fisher
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Sir,—Thank you for the opportunity to reply to Dr Stirton-Hopkins' letter.

Although the fentanyl and droperidol were flushed through the Wallace Y-can, the propofol appears to have been given immediately after the atracurium. While the "barking cough" during the atracurium injection suggests that this agent may have been responsible for the ensuing events, it is possible that an effect similar to the systemic aggregate anaphylaxis [1] which may occur with the mixing of thiopentone and atracurium may also occur with propofol (pH 7.5–8.5) and atracurium.

The results from the N.A.A.R.A.S. demonstrate the difficulties that sometimes occur in working out the mechanism of an adverse reaction. It is possible that an adverse response to propofol may be reported in the future when this agent has been in use for a longer period of time; the occurrence of life-threatening clinical anaphylaxis does not appear to be related to the ability of the drugs to release histamine [2].

I have perhaps been fortunate in that, during my 38 years of anaesthestic practice, I have had to deal with a life-threatening reaction to i.v. agents on only two occasions. Both occurred in healthy middle-aged female patients who had been given Althesin and fazadinium. One had a history of allergy and the other had been given the same drugs without difficulty 1 year previously. My clinical experience supports the opinion of Fisher, Outhred and Bowey that modification in anaesthetic techniques based on a history of allergy, atopy or asthma is unlikely to reduce the likelihood of severe clinical anaphylaxis.

I agree with Dr Stirton-Hopkins that the administration of adrenaline must not be delayed in severe anaphylactic reactions, and I would like to congratulate him on his successful management of this difficult emergency.

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Penmaenmawr

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ANAESTHETIC MANAGEMENT OF ACHONDROPLASIA

Sir—I have read with interest the article by Kella, Fening and Obiaya [1] entitled "Anaesthetic Management of Achondroplasia". The authors state that the literature is scanty concerning the anaesthetic management of achondroplastic patients, and refer to Mather's description of laryngoscopy and intubation as difficult in achondroplastic subjects [2]. I should like to draw attention to our article "Anaesthesia for the Achondroplastic Dwarf" [3] in which we reviewed the literature and found only two other articles which mentioned the management of the achondroplastic [2,4]. In 36 anaesthetics we observed, as did the present authors, that airway management was not difficult. We also noticed that drug doses based on weight resulted in no differences in clinical response in the achondroplastic patient when compared with the non-achondroplastic patient and agreed with the finding of Walts, Finerman and Wyatt [4] that weight, rather than years, was a more appropriate guide to tracheal tube size.

As far as I am aware, our series, although small in number, remains the largest series to date on the anaesthetic management of a patient with achondroplasty.

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CONTINUOUS I.V. INFUSION OF LABETALOL FOR POSTOPERATIVE HYPERTENSION

Sir,—Drs Chauvin, Deriaz and Viars [1] presented an interesting study of labetalol as a means of suppressing postoperative hypertension. Their study concentrated on the haemodynamic effects of a loading dose of labetalol 1.5 mg kg^{-1}, followed by an infusion of 0.2 mg kg^{-1} h^{-1}, but also provided data on plasma concentrations from which the clearance of the drug can be deduced. In their introduction and discussion, they imply that Dagnino and Prys-Roberts [2] published pharmacodynamic and pharmacokinetic data on infusions of labetalol. We wish to correct any misinterpretation of this statement. In that paper, we applied isoprenaline dose–response curves as a means of quantifying the pharmacodynamic effects of a number of beta-adrenoceptor antagonists, including labetalol administered by i.v. infusion.

In a separate study [3], we described the fuller relationship between the pharmacokinetic and dynamic effects of infusions of labetalol, relating the degree of beta-receptor blockade (as determined by the chronotropic dose of isoprenaline CD25) to the plasma concentration of the drug, rather than simply to the infusion rate. As part of this latter study we determined the clearance of labetalol after 24 and 48 h of infusion at a constant rate. We found the median value to be 11 ml kg^{-1} min^{-1} (range 5.8–24.7), a value very similar to that quoted by Chauvin and his colleagues.

We found that an infusion of labetalol 0.15 mg kg^{-1} h^{-1} caused sufficient hypotension to decrease urine output in a number of our patients in the intensive care unit. For this reason, we would caution against use of the dose recommended by Chauvin and his colleagues (0.2 mg kg^{-1} h^{-1}) for more than the 5.5 h for which they studied their patients.

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J. Dagnino
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Sir,—We agree with Professor Prys-Roberts and Dr Dagnino that the rate of infusion of labetalol (0.2 mg kg^{-1} h^{-1}) was too high. We calculated the infusion rate in order to obtain a steady state plasma concentration (C^{ss}) of 170 ng ml^{-1} on the basis of a clearance value of 20 ml kg^{-1} min^{-1} determined by previous pharmacokinetic studies after bolus i.v. injection [1]. In fact, the mean clearance value calculated in steady state conditions was lower than that used in our pharmacokinetic model and this explains why the measured C^{ss} was greater than the predicted one. In clinical practice, it is necessary to start the infusion at a slower rate—between 0.07 and 0.15 mg kg^{-1} h^{-1} and, as for other drugs, a gradual titration is required in order to normalize arterial pressure. In some patients, the effective infusion rate of labetalol is higher than 0.15 mg kg^{-1} h^{-1}. This may be consistent with the findings of Fell, Chmielewski and Smith [2] who noted that plasma noradrenaline concentrations were increased during the late period after operation. Such a high degree of resting sympathetic drive may require an increase in the infused dose of the β-adrenergic blocking agent to block adrenergic receptors. This was probably the case in our study, in which neither bradycardia nor hypotension was observed.

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UNCONSCIOUS PERCEPTION DURING ANAESTHESIA—COMMENT ON STATISTICS

Sir,—Wilson and Spiegelhalter [1] criticize Bennett, Davis and Giannini [2] on their statistics. When comparing 9/11 with 9/21, they say $P = 0.08$, not 0.05 as Bennett claims. Two comments are needed:

(1) If Dr Wilson is correct we are only 92% confident that this is a real difference, whereas by convention we need 95% confidence. Clearly, whichever figure is correct, we should draw the same conclusion—namely, that this interesting finding could well be genuine and needs verifying in a larger study. If the same percent results occurred with two samples of approx. 20, it would be highly significant by any test.

(2) We all applaud Dr Wilson's plea for good statistics—it is the only objective way to measure the strength of the evidence. Unfortunately, he himself has used a version of Fisher's exact test, which many of us cannot accept. Apart from anything else, in certain instances it can give impossible P values greater than 1. This has been discussed in detail elsewhere [3].

The problem lies not in the maths, which is elementary, but in what we mean by probability. To judge this, a research-worker is as well placed as a statistician (perhaps better, since we have to act on our conclusions). The classical tail area idea works perfectly for the t test, but it is never going to work for Fisher's test. The statistical establishment seems unwilling to get to grips with this problem. Anyone who cares about research and who has accepted the conventional versions hitherto is referred to Cormack [3].

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BOOK REVIEWS

Advances in Oxygen Monitoring. Edited by K. K. Tremper and S. J. Barker. *International Anesthesiology Clinics*, Vol. 25, No. 3. Published (1987) by Little Brown & Co., Boston. Pp. 240; illustrated.

Oxygen is essential to life and the ability to monitor oxygenation in various tissues has contributed greatly to our understanding of the physiological changes in disease. This latest volume of *International Anesthesiology Clinics* includes contributions from scientists and clinicians who have been at the forefront of the development and investigation of the various techniques for oxygen measurement.

Appropriately, the first chapter is by Leland Clark on the historical background and thought processes that led to his development of the Clark oxygen electrode. The use of this electrode in transcutaneous and conjunctival oxygen measurements is considered in succeeding chapters. The theory and value of pulse oximetry are dealt with succinctly by Jonas Pologe and the editors, respectively. The editors have also reviewed intra-arterial oxygen tension monitoring, a technique which appears more promising with the development of the fluorescence-based optochemical detectors or optodes. The theory of this interesting new technique is explored by Opitz and Lubbers. The volume ends with a review by Frans Jobis-Vanderliet of his NIROS scope which estimates cerebral oxygenation by measurement of the redox state of the cytochrome system by the absorption of near infra-red light.

Accounts written by pioneers often give greater insight, but their conclusions may be presented in a partisan fashion. This is the case with several of the chapters in this volume, and an overall view of the relative merits of the techniques would have been helpful. Nevertheless, the book can be recommended to those seeking an up to date account of this important subject.

C. D. Hanning

Anesthesia and Transplantation Surgery. Edited by B. R. Brown jr. Published (1987) by F. A. Davis Company, Philadelphia. Price £27.38.

Transplantation of organs such as the heart, liver and kidneys is no longer experimental and is becoming widespread, not only in the U.S.A., but also in the United Kingdom. This book has been written primarily for those involved in the anaesthetic care of patients undergoing such procedures. The knowledge it contains is, however, valuable for those not actively involved in this field, who may have to care for one of the increasing number of patients with a transplanted organ who require anaesthesia for a coincidental and unrelated procedure. Such a book on this subject is, therefore, both timely and appropriate. It contains 10 chapters written by 16 expert authors.

The first chapter is written jointly by a Professor of Law and the Chief of a Forensic Sciences Section at the University of Arizona College of Medicine. Although this is a very detailed chapter and relates to a legal system different from our own, it makes interesting reading. After a brief introduction, the first section of this chapter discusses, not surprisingly in the light of the current medico–legal climate in America, "Negligence or Malpractice" and then goes on to discuss Strict Liability before discussing organ procurement programmes, including the different types of organ donation possible and their legal pitfalls. There are other interesting sections, including those on the sale of organs and informed consent. Hopefully, the problem it discusses in this chapter will not find their way across to this side of the Atlantic. The next chapter deals with the perioperative management of the organ donor and is an excellent review of the physiology, maintenance and procurement of organ donors.

The next four chapters all deal with heart or heart–lung transplantation. The first of these chapters, entitled "Cardiac Transplantation: Recipient Selection Criteria and Pathophysiology and Management of Advanced Heart Failure," is almost entirely devoted (after a brief description of selection criteria) to the pathophysiology of heart failure and its treatment. It is an extremely well written, up to date guide on this subject. The next chapter, "Managing the Cardiac Transplant Patient" is a broad overview of cardiac transplantation and describes the transplant team, operative procedures, postoperative care, rejection, infection and discharge planning. The penultimate chapter in this section deals with anaesthesia for cardiac transplantation and covers some areas that had already been described, including recipient selection and donor management. Unfortunately, it devotes only 4½ pages to the actual anaesthetic technique. However, there is a useful section on the physiology of the transplanted heart and anaesthesia for patients after cardiac transplantation. The fourth of these chapters deals with anaesthesia for combined heart and lung transplantation. There is a good description of primary pulmonary hypertension and Eisenmenger's syndrome. There is, again, special reference to the donor criteria and management and the donor operation before the anaesthetic and surgical techniques are described. The physiology of the transplanted heart and the transplanted lung are described.

The seventh chapter is devoted to the history and development of the artificial heart. Although this part of organ transplantation is still in its infancy, this chapter is well illustrated with case reports and a fascinating review of the pharmacology of vasoactive drugs in patients with an artificial heart *in situ*.

Liver transplantation is described in chapter 8. I found this the most disappointing part of the book. Only 25 pages were devoted to the topic and are woefully inadequate. There is an adequate description of the anaesthetic techniques, including the use of bypass in both paediatric and adult patients. However, there is little on patient selection and only one small paragraph on postoperative care. There is virtually nothing on the altered pharmacology seen in these patients. The following chapter, on renal transplantation, contrasts with this. It covers the history of renal transplantation, describes both haemodialysis and peritoneal dialysis, defines suitable recipients and contains an excellent review on the alteration in drug action in patients with renal failure. The problems of harvesting kidneys and the various pathophysiological conditions that may affect the perioperative management in these patients are also described.

The final chapter in the book seems a little out of order, and is devoted to immunosuppression following cardiac transplantation. It describes its history and current U.S. procedures for the management of immunosuppression following cardiac transplantation.

The lack of space devoted to liver transplantation and the absence of any mention of pancreatic transplantation are disappointing. This results in an inbalance of contents, with too much emphasis on cardiac transplantation. Despite this, I thought this was a well written book with some very clear descriptions in it. The sections on management, on the pathophysiology and treatment of chronic heart failure, vasoactive drugs in the transplanted heart and most of the section on the perioperative management of patients for renal transplantation are particularly good. There was some duplication, in particular with regard to the selection and management of organ donors, immunosuppression and recipient selection. Each chapter is well referenced and the book is a good summary of the history and our current knowledge of anaesthesia for transplant surgery. It would be a valuable addition to the library of most departments, both for those candidates about to sit examinations and for others who may wish to refer to it when faced with a patient who has a transplanted organ.

G. R. Park

Sickle-Cell Anemia and Thalassemia: A Primer for Health Care Professionals. By R. G. Huntsman. Published (1987) by the Canadian Sickle Cell Society, PO Box 13156, Station A, St John's, Newfoundland A1B 4A4 (available by post). Pp. 223. Price £5.00.

The advice in this slim volume on the anaesthetic management of sickle cell disease is short but practical, and those seeking details of techniques will have to search elsewhere. The value of this book is in the concise but comprehensive coverage of the haemoglobinopathies, both common and rare. The first section outlines clinical management and includes practical information on matters such as flying. The second section deals with the biochemistry and laboratory investigation. A comprehensive glossary is provided for the lay reader.

The book is written in a lively style by an acknowledged expert. It is a useful (and inexpensive) initial reference source and is recommended to those who occasionally treat patients with haemoglobinopathies.

C. D. Hanning

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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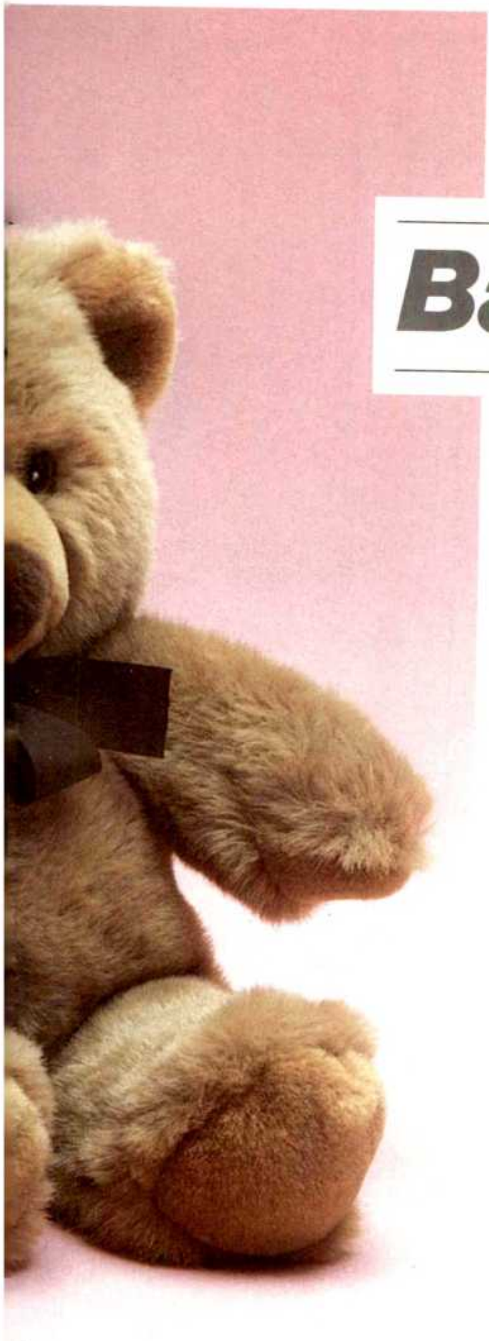

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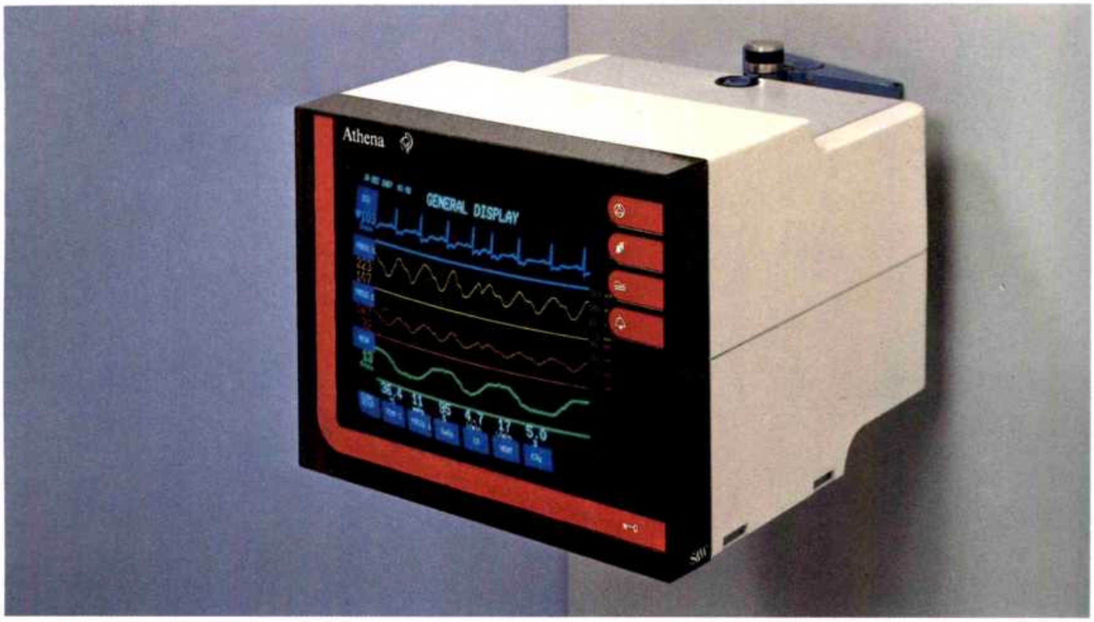

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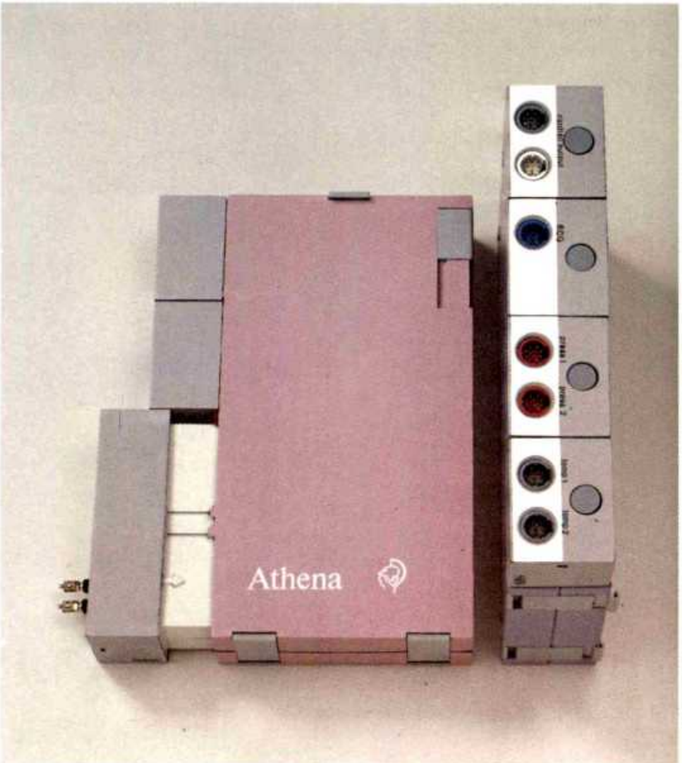

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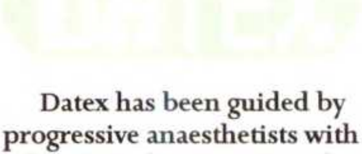

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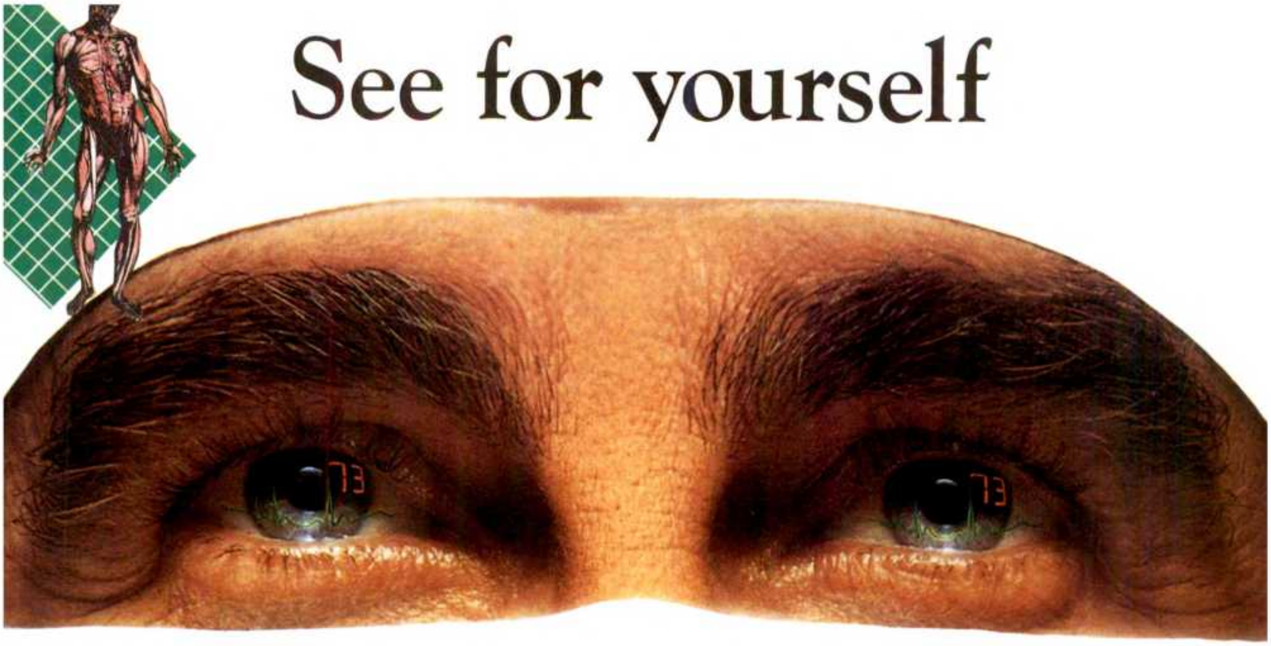

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results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

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Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

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(TABLE III near here)

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

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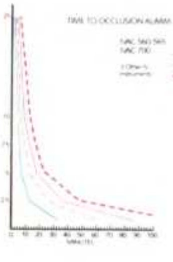

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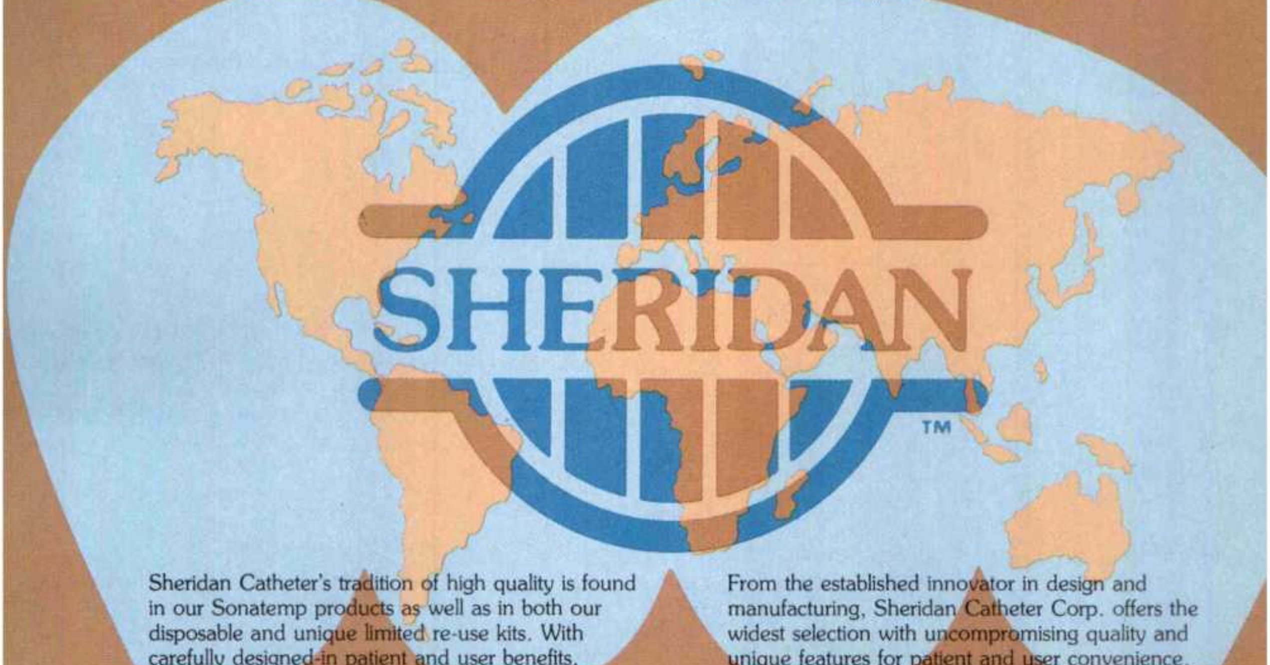

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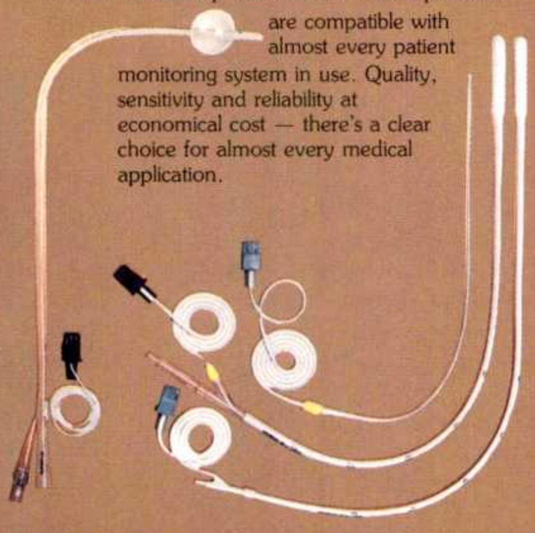

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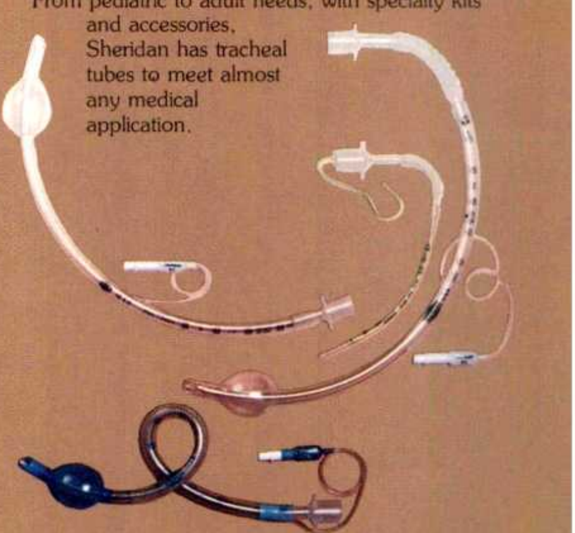

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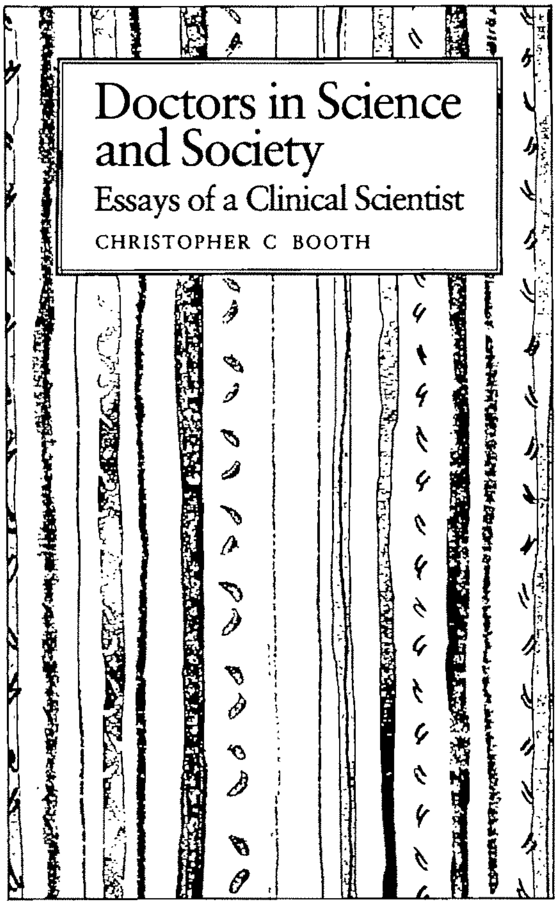

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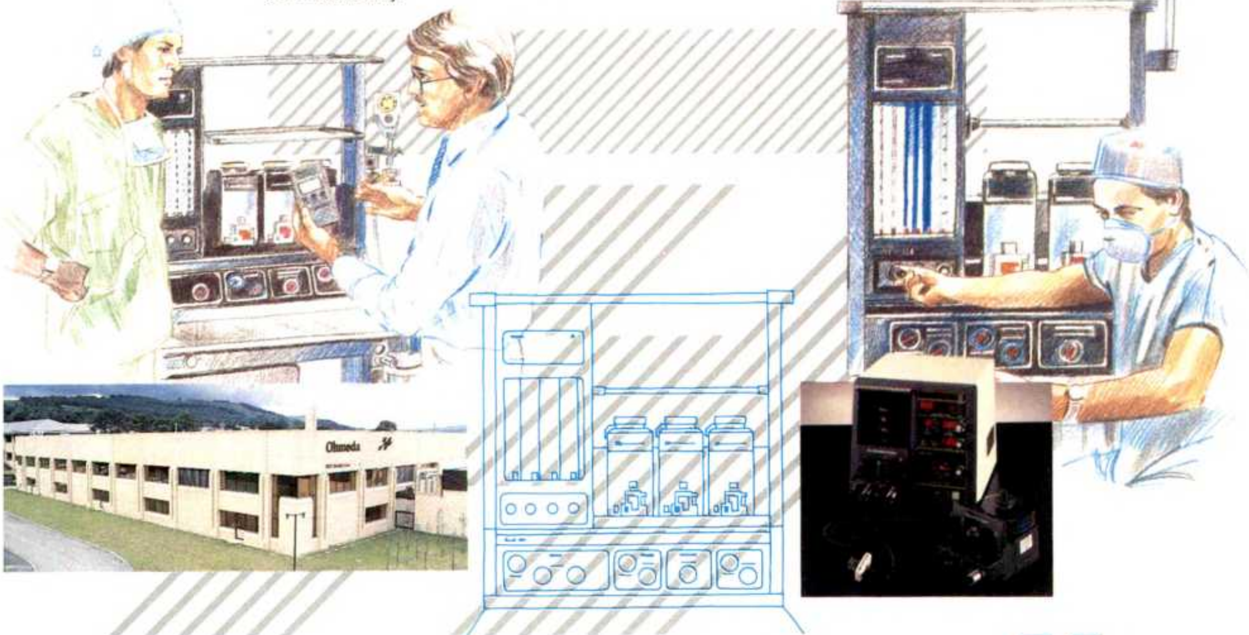

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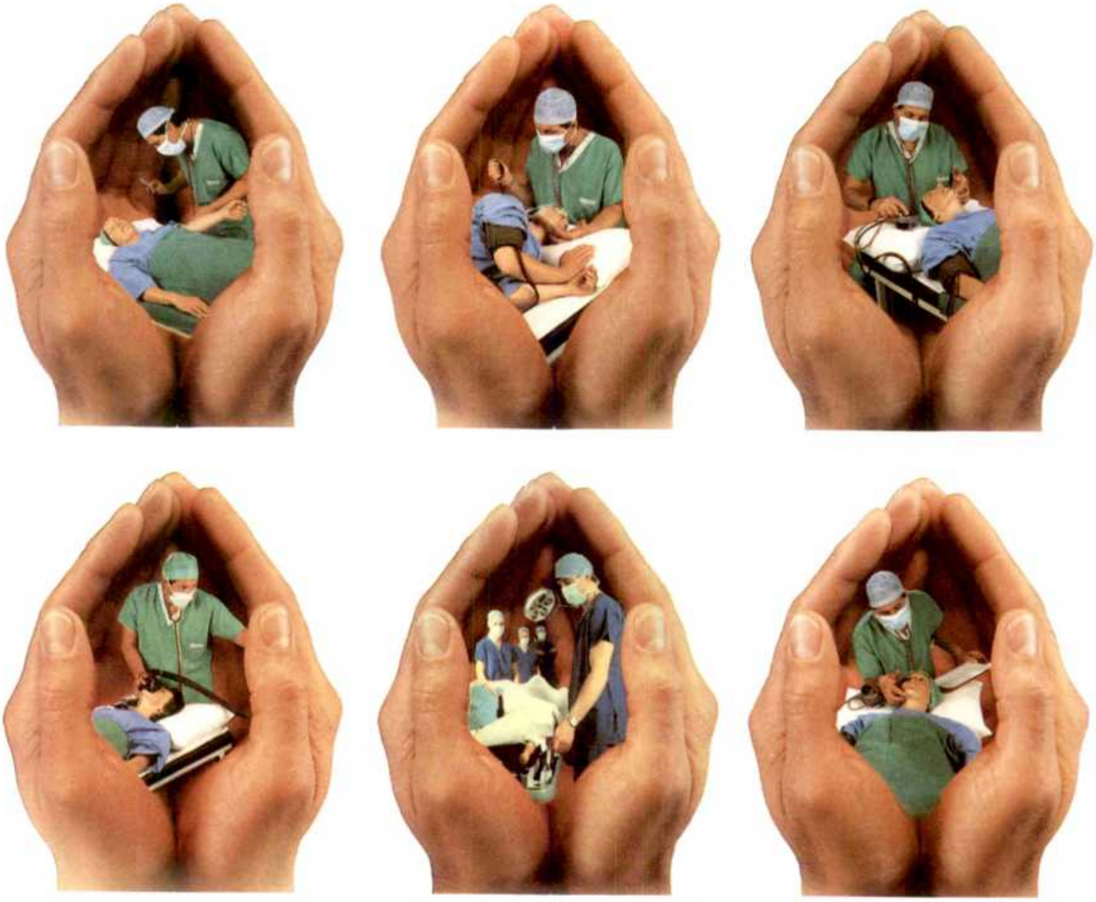

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 60, No. 6 MAY 1988

EDITORIALS

NINTH WORLD CONGRESS OF ANAESTHESIOLOGY

This issue of *British Journal of Anaesthesia* marks the occasion of the 9th World Congress of Anaesthesiology in Washington. The frequency of world congresses dictates that each national society of anaesthetists has the opportunity of organizing such an international meeting on only one occasion in a life-time. This opportunity frequently acts as an incentive and we are confident therefore that, under the auspices of the American Socity of Anesthesiologists, an outstanding meeting has been organized with great efficiency. As a result, it is anticipated that those who are fortunate enough to attend the Congress will enjoy an academic programme which provides intellectual nourishment of a high order and social activities which combine hedonism with culture.

The additional printing on our front cover is designed to commemorate the Congress, but does not signify any special selection of manuscripts for this issue. The contents have been determined by the emergence of papers through normal editorial processing. It will be immediately obvious that the number of manuscripts originating from outside the U.K. exceeds the number of British papers—we have authors from Canada and the United States, Western Europe, Scandinavia, the Republic of Ireland and Australia, and only seven manuscripts from the United Kingdom. This reflects the international nature of our *Journal*, which is reflected also in the fact that the number of subscribers resident outside Britain greatly exceeds that within the country. Thus, to some extent, the title "British" is misleading as it applies only to the location of the immediate editorial team and publishers.

British Journal of Anaesthesia is the oldest and largest independent journal of anaesthesia in the world. The majority of other large anaesthetic journals are connected with institutions, clubs or societies of anaesthesia, the functions of which are clearly and immediately discernible to their members. However, in recent years, *British Journal of Anaesthesia* has also developed activities in addition to those involved in the publication of scientific manuscripts. At the time of this World Congress, it seems appropriate to us for these wider aspects of the *Journal's* affairs to be revealed before our readers and subscribers. We have therefore invited the Chairman of the Editorial Board to produce an accompanying editorial which, in the context of our 65th anniversary, discourses on these topics.

Graham Smith
Editor

SIXTY-FIVE AND GOING STRONG!
BRITISH JOURNAL OF ANAESTHESIA REACHES ANOTHER LANDMARK

This year *British Journal of Anaesthesia* is paying a visit to the United States, to the World Congress at Washington. The programme committee has agreed that we may hold a session entitled "Going into Print", where issues relating to modern journal publication will be aired. Specific views will be presented by members of our Board, aided by discussion with editors from other leading anaesthetic journals on the correct approach to preparing and submitting manuscripts.

British Journal of Anaesthesia is, of course, no stranger to the United States. In addition to our valued contributors, readers and subscribers within the U.S., we are proud that our founder, in 1923, and first editor, H. M. Cohen, was an American. He qualified in New York and served with the U.S. Army as a doctor, but settled in Manchester where the Journal was published from 1923 to 1974. From the start, American interest and participation was intense with the names of Gwathmey, Donovan, Guedel and especially McKesson prominent. They exchanged anaesthetic recipes, social news and also, occasionally, gossip. For example, the communications following the deaths of S. R. Wilson (Secretary to the Board) and Howard Jones, while respectful, make rivetting reading and would be considered bad taste by today's standards.

By the late 1920s, leading figures from British and American anaesthesia had exchanged visits and the *Journal* carried photographs of the parties on board ship. In 1927, the Board of *British Journal of Anaesthesia* received a splendid diploma from the International Anesthesia Research Society (IARS) in recognition of its services to the specialty. In all this, the hand of F. W. McMeechin, the great international protagonist of anaesthesia and founder of the IARS (and also our senior contemporary *Anesthesia and Analgesia*) is evident. In addition to those of Cohen and Wilson, the names inscribed on the diploma include Boyle, Buxton, Blomfield and Fairlie. Recently, the Board has located a copy of the diploma and will be taking it to Washington in the belief that it may have some currency if we find the right quarter!

It is normal policy to allow our ship to sail without making an exhibition of the engine room. However, in response to the Editor's request in the preceding editorial, some aspects of our Board's work are presented here and they are unique in anaesthesia.

The Editorial Board of the *Journal* has a defined size and elects itself according to a precise constitution, having regard to the need to recruit the best academic talent in the U.K. and, increasingly, an appropriate range of specialist advice. From time to time, the Board has considered the case for establishing an international board. So far, this idea has been set aside because of the potentially high cost of arranging meetings. In practice however, the Board receives help and advice from distinguished anaesthetists in many countries, so that there is an informal group of "friends" of the *Journal*. Service on the Board is entirely voluntary.

The Board elects the editors, usually from its own ranks. In the past 65 years there have been only seven editors, two (E. Falkner Hill and T. C. Gray) in partnership for part of their period of office. Now Graham Smith succeeds William Fitch in the role.

The Board corporately owns the *Journal* and acts through three trustees, whose actions are governed by U.K. laws on trusteeship. Thus there is no question of any individual owning an asset. For more than 60 years, the *Journal* was produced for the Board by publishers who acted in a normal commercial role, bearing any financial risks and providing the Board with sufficient funds for editorial purposes.

In the early 1980s, the standing of the *Journal* was sufficiently secure to enable the Board to accept responsibility for its financial fortunes. Through our present contract with PSP (the publishing division of the British Medical Association) each component of the publication process is undertaken for an appropriate fee, but the Board retains any profit (or bears any loss). Thus we have total control of costs and any surplus generated may be applied, after professional advice, to charitable activities in anaesthesia. The *Journal* is registered as a charity under U.K. law and is thus exempt from taxation. The principal charitable activity is, or course, production of the *Journal*.

Within the past 3 years, we have organized annual writing workshops for doctors in training, the entire cost being borne by the Board provided the registrant submits in advance a manuscript suitable for dissection. We have provided the Association of Anaesthetists of Great Britain and Ireland with funds to cover the total cost of furnishing the "*British Journal of Anaesthesia*" library at its new headquarters in 9 Bedford Square, London. We were pleased to donate to the lecture fund established in memory of our late colleage Gordon McDowall. Furthermore, we have established a research fellowship and the first advertisement for this post attracted strong competition. Recently we invited applications for a number of short-term travelling fellowships to enable young anaesthetists from other countries to visit selected training centres in the U.K.

It is not our intention to generate large profits, since our primary purpose is the dissemination of knowledge through the *Journal*. However, we are proud that the current stewardship of our prized heritage is being turned more effectively to the wider academic purposes of the specialty of anaesthesia.

What are the special challenges facing us now? The Board and its Editors are acutely aware of the need to balance the essential role of the *Journal* as a vehicle for good quality reports of laboratory and clinical research with the provision of high grade review material for the general reader. We regard with disappointment the emergence of populist material from poorly identified sources which is intended to offer light reading for professionals. This usually lacks the talent to achieve quality and instead resorts to a dangerous pseudo-science, amounting at times to misleading information. Sadly, the revolution in printing techniques will result in such risks to our professional standards remaining with us for the foreseeable future.

We are conscious also of the implications of technological change for our own *Journal*. The Board is concerned that in recent times the interval between receipt of manuscripts and publication has become unacceptably long. A priority now is to ensure, after careful revision of our editorial and publishing processes, that these delays are at an end. *British Journal of Anaesthesia* was the first journal in the specialty to appear monthly, in 1955, and did so to expedite publication. The introduction of new technology can, and has already started to, achieve the same end.

In our special anniversary year we send greetings to friends and subscribers throughout the world. To our friends in the United States we wish, in addition, success in the forthcoming 9th World Congress.

Alastair A. Spence
Chairman of the Editorial Board

Br. J. Anaesth. (1988), **60**, 608–613

POSTOPERATIVE ANALGESIA WITH FENTANYL: PHARMACOKINETICS AND PHARMACODYNAMICS OF CONSTANT-RATE I.V. AND TRANSDERMAL DELIVERY†

F. O. HOLLEY AND C. VAN STEENNIS

SUMMARY

We have investigated the use of constant-rate delivery of fentanyl by i.v. and transdermal routes for the treatment of pain after major surgery. Forty-five males, ASA I–III, received in a double-blinded fashion either placebo ($n = 6$) or fentanyl ($n = 39$) i.v. at one of four dose rates (25, 50, 100 or 125 $\mu g\ h^{-1}$). Stable serum concentrations of fentanyl were produced by the end of surgery and were maintained for a total of 24 h. Calculated clearance of fentanyl was 1.05 ± 0.38 litre min^{-1} and was not related to weight or age. Both the 100- and 125-$\mu g\ h^{-1}$ dose rates produced significant analgesic efficacy as assessed by postoperative morphine requirements. Mean serum concentrations of fentanyl in these groups were 1.42 ± 0.14 (SD) and 1.90 ± 0.30 ng ml^{-1}, respectively. One of 10 patients receiving fentanyl 100 $\mu g\ h^{-1}$ and three of nine patients receiving 125 $\mu g\ h^{-1}$ had evidence of respiratory depression. Eight additional patients were treated with a transdermal drug delivery system containing fentanyl (TTS-fentanyl). Steady-state serum concentrations in this group were 2.15 ± 0.92 (SD) ng ml^{-1}. Postoperative morphine requirements were minimal (< 0.5 mg h^{-1}) and Pa_{CO_2} remained acceptable in all patients. Serum concentrations of fentanyl increased slowly (15 h to plateau) and decreased slowly (apparent half-life, 21 h). We conclude that delivery of analgesic doses of fentanyl is feasible by the transdermal route.

To determine if fentanyl would be suitable for transdermal drug delivery, we first tested the efficacy and safety of fentanyl as a postoperative analgesic when administered by constant-rate i.v. infusion. Since fentanyl has been used primarily during operations, information on appropriate postoperative analgesic doses and concentrations has not been available until recently [1]. In the same postoperative pain model, we subsequently tested the first transdermal delivery systems designed to produce analgesic serum concentrations of fentanyl for a prolonged period of time.

PATIENTS AND METHODS

We studied 53 male patients, ASA status I–III, undergoing surgery expected to produce severe postoperative pain. Patient exclusions included those weighing less than 50 kg or more than 110 kg, those with liver enzyme abnormalities, history of heavy alcohol consumption, psychiatric illness, neurological deficit, history of regular opioid use, or those requiring mechanical ventilation. After institutional review board approval and informed consent, the first 45 of these patients were randomly allocated in a double-blind fashion to one of five treatment groups (groups I–V) (table I). After premedication with diazepam 5–15 mg orally and atropine 0.6 mg i.m., patients were given an i.v. loading dose of fentanyl or placebo (table II), and an i.v. infusion was begun with one of four doses of fentanyl or placebo (table II). Anaesthesia was then induced with thiopentone 2–4 mg kg^{-1}, the trachea was intubated after suxamethonium 1.5 mg kg^{-1}, and anaesthesia was

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TABLE I. *Patient data (mean ± SD)*

Group	Surgical procedure	Age (yr)	Weight (kg)	Height (cm)
I	Lumbar laminectomy (2), lumbar fusion, laparotomy (3)	53 ± 13	76 ± 7	183 ± 5
II	Lumbar fusion (2), knee replacement (2), shoulder capsule repair, laparotomy (4), thoractomy	54 ± 12	76 ± 12	175 ± 8
III	Lumbar laminectomy (2), lumbar fusion, knee replacement (2), knee arthrotomy (2), open tibial fixation, laparotomy, thoracotomy	44 ± 15	81 ± 16	180 ± 5
IV	Lumbar fusion (2), posterior cervical fusion, knee replacement, laparotomy (5), thoracotomy	56 ± 12	80 ± 17	175 ± 8
V	Lumbar fusion (2), shoulder capsule repair, open tibial fixation, laparotomy (5)	54 ± 12	77 ± 5	175 ± 8
VI	Lumbar fusion, thoracotomy (7)	58 ± 7	80 ± 18	180 ± 10

TABLE II. *Regimens of opioid doses*

Group	*n*	24-h fentanyl infusion	Fentanyl loading dose (i.v.)	Supplementary analgesic
I	6	Placebo	(Placebo)	Morphine 1–2 mg i.v.
II	10	25 μg h^{-1}	100 μg	Morphine 1–2 mg i.v.
III	10	50 μg h^{-1}	200 μg	Morphine 1–2 mg i.v.
IV	10	100 μg h^{-1}	400 μg	Morphine 1–2 mg i.v.
V	9	125 μg h^{-1}	500 μg	Morphine 1–2 mg i.v.
VI	8	TTS-fentanyl	300 μg	Morphine 1–2 mg i.v. in recovery room Morphine 4 mg i.m. up to every 2 h thereafter

maintained with 67 % nitrous oxide and 0.5–2.0 % enflurane in oxygen. Neuromuscular blockade, if needed, was achieved with pancuronium and antagonized with neostigmine and glycopyrrolate. The fentanyl (or placebo) infusion was continued into the postoperative period for a duration of 24 h.

After operation, a nurse-observer blinded to the dose of fentanyl administered asked patients at 1-h intervals to rate their pain on a 10-point scale from 0 (no pain) to 9 (severe pain). If pain was present, morphine was given, in increments of 1–2 mg at 10-min intervals until the patient no longer requested medication. Pain scores were recorded before the administration of each dose.

Blood was sampled from a radial artery catheter every 2 h for measurement of serum concentrations of fentanyl. In eight patients in groups IV and V, samples were obtained at 2, 4, 8, and 12 h after discontinuing the infusion, to estimate elimination half-life. Arterial blood-gas tensions were measured at 4–6 h intervals or more frequently if indicated clinically. The rate of ventilation was recorded hourly. Criteria for discontinuing the opioid infusion included an arterial Pa_{CO_2} exceeding 7.3 kPa, a ventilatory rate of less than 8 b.p.m., or extreme drowsiness.

The final eight (group VI) of the 53 patients received fentanyl transdermally for 24 h in an open study during the perioperative period. Fentanyl was delivered by an investigational transdermal drug delivery system, TTS-fentanyl (Alza Corp., Palo Alto, California) with a nominal delivery rate of approximately 100 μg h^{-1}. The transdermal system was applied to the patient's upper chest 2 h before induction of anaesthesia and left in place for 24 h. Patients received a loading dose of fentanyl 300 μg i.v. at induction, followed by the anaesthetic technique described above. Postoperative assessments were identical to those described above. For postoperative escape analgesia, morphine 4 mg i.m. was available on demand at 2-h intervals. Blood samples were obtained at 1-h intervals and at 2, 4, 6, 8, 10, 12, 24, 30 and 36 h after removal of the system for assay of fentanyl.

In order to obviate any adsorption of fentanyl

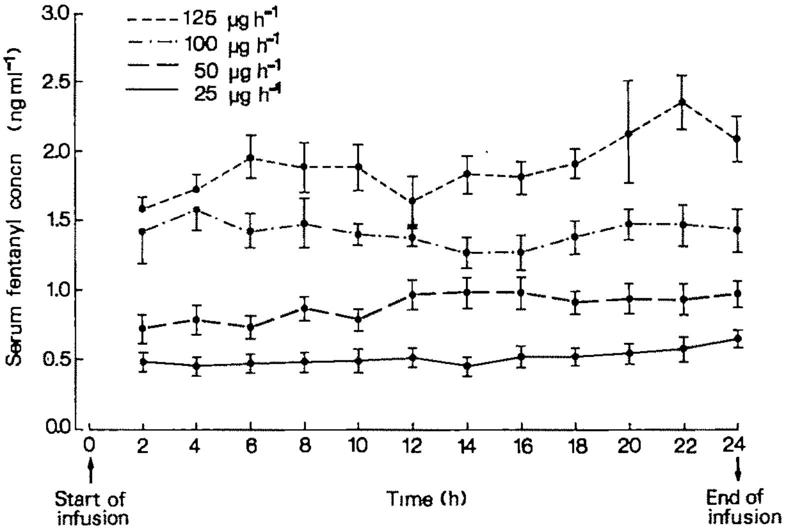

FIG. 1. Mean (±SEM) serum concentrations of fentanyl in 39 patients in groups II–V who received fentanyl i.v.

onto plastic or rubber during long-term contact, solutions were delivered from a glass syringe using an Autosyringe pump (Autosyringe Inc., Hookset, New Hampshire). Blood samples were stored on ice, allowed to clot, centrifuged, and the serum removed and stored at −12 °C until analysis. Serum concentrations of fentanyl were measured by radioimmunoassay as described by Michiels, Hendriks and Heykants [2], with the modification proposed by Schüttler and White [3]. This assay was sensitive to 0.25 ng ml⁻¹, with intra-assay and inter-assay coefficients of variation of 7 % and 7 %, respectively, at 1 ng ml⁻¹. Clearance was calculated from the formula:

$$\text{Clearance} = \frac{\text{Infusion rate}}{\text{Steady-state concentration}}$$

Elimination half-lives were estimated from mean patient data. Overall comparisons among multiple groups were made using analysis of variance with subsequent intergroup comparisons by unpaired t test, using the appropriate Bonferroni correction. Respiratory toxicity in group V was compared with that in groups I–IV, using a chi-square statistic with Yates' correction for continuity.

RESULTS

Patients in the six treatment groups did not differ significantly in age, weight, height or type of surgical procedure (table I). The mean duration of surgery, 3.6 h, also did not differ.

Pharmacokinetics—i.v. fentanyl

Serum concentrations of fentanyl were stable during the study period (fig. 1). The average intra-individual coefficient of variation was 23 % (range 12–59 %). The correlation coefficient be-

TABLE III. *Fentanyl pharmacokinetics (mean ± SD). *15–24 h serum concentration*

Group	2–24 h serum concentration (ng ml⁻¹)	12–24 h serum concentration (ng ml⁻¹)	Clearance (litre min⁻¹)
II	0.51±0.19	0.53±0.20	0.89±0.38
III	0.87±0.29	0.94±0.32	1.01±0.49
IV	1.42±0.14	1.37±0.28	1.26±0.27
V	1.90±0.30	1.97±0.40	1.09±0.19
VI	—	2.15±0.93*	—

TABLE IV. *Fentanyl pharmacodynamics (mean ± SD). *Significantly different from groups I–III (P < 0.05). **P < 0.01 by analysis of variance. † Significantly different from groups I–IV (P < 0.05)*

Group	Total MS over 24 h (mg)	Mean $P\text{CO}_2$ (kPa)	Mean $P\text{O}_2$ (kPa)	Dropout for toxicity
I	26±13	4.9±0.53	11.1±0.40	0/6
II	30±15	5.2±0.53	11.1±1.73	0/10
III	32±24	5.3±0.27	12.3±2.67	0/10
IV	16±13*	5.3±0.53	13.5±3.07	1/10
V	8±9*	6.4±1.47**	11.6±1.47	3/9†
VI	14±6	5.7±0.67	13.5±1.73	0/8

tween the mean 2–24 h concentration of fentanyl for each patient and the dose was 0.94.

There was no difference between mean serum concentrations of fentanyl for the 12–24 h and 2–24 h periods (table III). The former was used to calculate clearances, which did not differ significantly between groups II–V (table III). The mean fentanyl clearance for groups II–V was 1.05 ± 0.38 litre min^{-1}. There was no correlation between clearance of fentanyl and weight (weight range 50–110 kg; $r = -0.01$) or age (age range 24–68 yr; $r = 0.25$).

The mean elimination half-life in eight group IV and group V patients was calculated as 8.0 h.

Pharmacodynamics—i.v. fentanyl

The analgesic endpoint, or pain score at which the patient requested no further analgesic, was not significantly different in groups I–VI (mean 3.0), although it did vary from patient to patient (range 0–6).

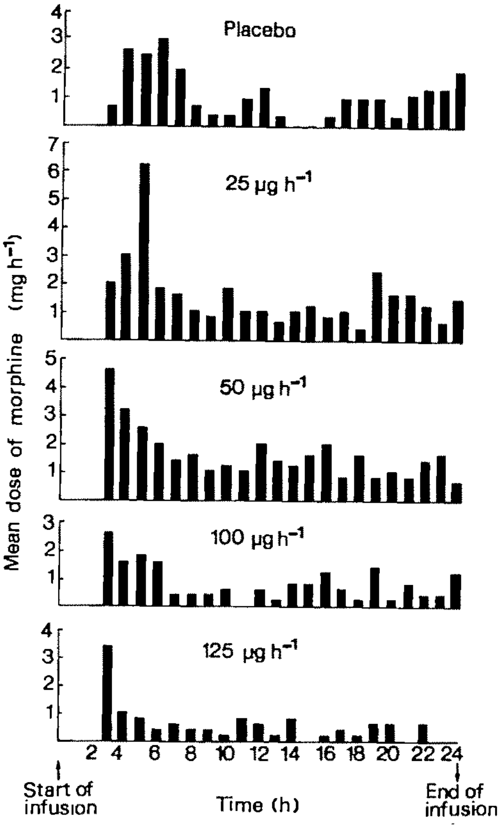

FIG. 2. Mean morphine dose in the five groups of patients receiving fentanyl i.v. No morphine was administered during surgery (hours 1 and 2). The higher early requirement (hours 3–6) represents analgesic stabilization in the recovery room.

Analgesic efficacy in groups II and III was not significantly different from group I (placebo), as assessed by the total amount of morphine required in a 24-h period (table IV). However, the entire relationship for groups I–V was significant by analysis of variance ($P = 0.026$). Therefore, groups IV and V were each compared with groups I–III combined, using a Bonferroni corrected t test, and a significantly lower morphine requirement was found.

The pattern of morphine requirements revealed greater consumption in the first few hours and thus represents analgesic stabilization in the recovery room (fig. 2). Subsequently, morphine consumption diminished, particularly in the two highest dose groups, where it was less than 1 mg h^{-1}.

Ventilatory rate was unhelpful in detecting hypercapnia: rates in patients with $Pa_{CO_2} > 6.7$ kPa ranged from 7 to 22 b.p.m. In patients with ventilatory rates of 10 or less, Pa_{CO_2} values ranged from 3.3 to 7.1 kPa. No patient in the study became unarousable or developed respiratory depression requiring naloxone. However, four patients were withdrawn from the study because of hypercapnia ($Pa_{CO_2} > 7.3$ kPa). In two patients, one each from groups IV and V, this occurred during recovery from anaesthesia, with the effects of enflurane as a possibly contributing cause. Fentanyl concentrations at the time were 1.3 and 1.8 ng ml^{-1}, respectively. In two additional patients, both in group V, hypercapnia developed gradually, and the studies were terminated early at 15 and 23 h with fentanyl concentrations of 1.4 and 2.6 ng ml^{-1}, respectively. Thus, in three of nine patients in group V the regimen failed.

Arterial oxygenation was satisfactory and did not differ in groups I–V (table IV). However, a significantly greater proportion of groups IV and V (74%) received supplementary oxygen for at least 12 h after operation in comparison with groups I–III (28%) because of $Pa_{O_2} < 9.3$ kPa, breathing room air in the recovery room. The majority of the study population were smokers.

The incidence of nausea and vomiting was low. In groups I–V, 24% of patients complained of nausea at some point, 11% vomited, and 9% received antiemetic medication (prochlorperazine 10 mg i.m.). There was no difference between groups.

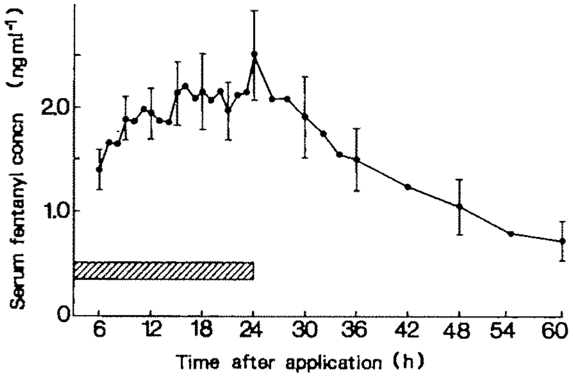

FIG. 3. Mean (±SEM) serum concentrations of fentanyl in the patients who received fentanyl transdermally. No data are shown until 6 h because the blood sampling schedule was not designed to characterize the serum concentration–time profile of the 300-μg loading dose. Cross-hatched bar represents administration of fentanyl.

Transdermal fentanyl

Mean serum concentrations of fentanyl in the eight patients treated with TTS-fentanyl (group VI) are shown after 6 h as the blood sampling schedule was not designed to characterize the serum concentration–time profile of the 300-μg loading dose. Serum concentrations did not reach a plateau until approximately 15 h after application of the transdermal fentanyl systems (fig. 3). The mean apparent half-life of fentanyl concentrations after removal of the transdermal system was approximately 21 h.

Although the patients with the transdermal system received a different postoperative analgesia regimen in an unblinded study, compared with groups I and V, their additional morphine requirements, 14±6 (SD) mg, are reported in table IV for comparative purposes. Sixty percent of this requirement was needed during the recovery room period, before fentanyl concentrations had reached a plateau; thus an average of one to two supplementary injections of morphine 4 mg i.m. were required over the succeeding 16-h period. The mean Pa_{CO_2} was 5.7±0.67 kPa (SD) in group VI, and no patient was withdrawn from the study on account of respiratory depression.

DISCUSSION

The clearance of fentanyl of approximately 1 litre ml^{-1} found in this study agrees well with that reported in studies involving constant-rate fentanyl infusions [1, 4] and also with that determined in bolus dose studies in surgical patients and volunteers [5, 6].

Our data show that there is no basis for correcting fentanyl clearance for body weight in adult males (50–110 kg), confirming the views of Mather [7]. This simplifies the provision of postoperative analgesia with continuous fentanyl administration. In a study of fentanyl pharmacokinetics, Scott and Stanski [8] have also shown that the volume of distribution of fentanyl is unrelated to body weight in adult males.

The elimination half-life of fentanyl of 8 h is longer than that reported elsewhere [5]. It is possible that the use in our study of a larger dose of fentanyl (with ability to measure plasma concentrations for longer) and the use of prolonged administration (with less interference with the terminal phase by drug distribution) has enabled us to define the terminal phase more clearly than in previous studies which have used bolus doses. Scott and Stanski [8] sampled for 24 h after a rapid fentanyl infusion and calculated an elimination half-life value similar to that reported here. Large inter-patient variability in the pharmacokinetics of fentanyl, noted here, has been reported elsewhere [5, 9].

In the patients who received fentanyl transdermally, we have demonstrated plateau serum concentrations comparable to those described elsewhere [10] and to those produced in the highest dose group (group V), who received the drug i.v. The slow decline of fentanyl concentrations may be explained by continued absorption from a skin depot of the drug after removal of the transdermal system, as may be expected for a lipid-soluble drug such as fentanyl [11]. Uptake by a skin depot may also explain the slow attainment of a plateau (approximately 15 h) in the transdermal group. Other reports [10, 12, 13] have described a similar pattern of serum concentrations of fentanyl after transdermal administration.

In the patients given i.v. infusions, significant analgesic efficacy became evident at a fentanyl dose of 100 $\mu g\ h^{-1}$ as assessed by a reduction in morphine requirements. Nimmo and Todd [1] have shown that an infusion rate of 86 $\mu g\ h^{-1}$ was effective in a group of females undergoing hysterectomy. In our study, a dose of 125 $\mu g\ h^{-1}$ reduced morphine requirement even further, but this was achieved at the cost of respiratory depression. Hypercapnia is a relatively late sign of respiratory depression with opioid analgesics. In a study of carbon dioxide rebreathing after administration of fentanyl, a Pa_{CO_2} of 7.3 kPa correlated with a carbon dioxide response of only 25% of normal [14]. Thus, in our study, fentanyl infused at 125 μg h^{-1} produced an unacceptable incidence of respiratory depression. It is possible that such a high dose might be tolerated better after elimination of respiratory depressant anaesthetics, as two of four of our patients were withdrawn from the study during emergence from anaesthesia. It is noteworthy that Duthie, McLaren and Nimmo [4] found that fentanyl in an infusion rate of 100 μg h^{-1} i.v. was effective and safe when given by prolonged constant rate infusion for the relief of pain after major surgery.

In the transdermal fentanyl group, plateau serum concentrations were slightly, although not significantly, higher than those achieved in the highest dose i.v. group. Thus, it would appear that the transdermal route is capable of delivering analgesic doses and concentrations of fentanyl. Morphine requirements to achieve the same analgesic endpoint in the transdermal group were similar to those required by the group given fentanyl 100 μg h^{-1} i.v. All eight patients who received fentanyl transdermally completed the regimen successfully without overt respiratory depression.

In summary, we have studied the pharmacokinetics and pharmacodynamics of a constant-rate i.v. fentanyl infusion for analgesia after major surgery. In our patient population, an infusion rate of 100 μg h^{-1} appeared to be the maximum, safe dose. Similar plateau concentrations of fentanyl were produced by a new transdermal delivery system and this was associated with comparable analgesia. Following application and removal of transdermal fentanyl, serum concentrations of the opioid increase and decrease relatively slowly, probably because the skin acts as a depot. The advantage of this method of application is that the onset of the side effects and toxic effects is slow. The disadvantage is that, when the method is used as the sole means of providing analgesia, early application is required to anticipate the late development of pain.

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PLASMA FENTANYL CONCENTRATIONS DURING TRANSDERMAL DELIVERY OF FENTANYL TO SURGICAL PATIENTS

D. J. R. DUTHIE, D. J. ROWBOTHAM, R. WYLD, P. D. HENDERSON AND W. S. NIMMO

Pain after surgery is treated commonly with intermittent i.m. opioids, but this regimen is often ineffective. Infrequent administration of the drug and variability of drug absorption and patient response are important causes of failure to achieve satisfactory analgesia.

Rate-controlled i.v. administration of opioids [1–3] may improve analgesia by ensuring drug delivery and minimizing variability of absorption [4, 5]. However, this regimen may require costly electronic apparatus.

Transdermal delivery systems are simple to use and permit reproducible and reliable administration of drugs [6, 7]. Glyceryl trinitrate, hyoscine, clonidine and oestrogens can be administered transdermally [8–11]. Fentanyl has now been formulated into a transdermal therapeutic system (TTS-fentanyl, Alza Corporation).

We have measured plasma fentanyl concentrations in surgical patients given fentanyl by this transdermal system and compared them with data published previously from a matched group of patients receiving fentanyl infusion i.v. [12].

PATIENTS AND METHODS

After Ethics Committee approval and informed written consent, 34 patients aged 18–70 yr, undergoing abdominal surgery were studied. All patients weighed 50–100 kg and none had clinical evidence of hepatic, psychiatric, renal or respiratory disease.

SUMMARY

Plasma fentanyl concentrations were measured during and after transdermal fentanyl delivery in groups of patients undergoing general surgery. At 8 and 12 h, concentrations did not differ from those observed in a matched group of patients receiving fentanyl by i.v. infusion. At 24 h, concentrations were significantly lower in one of the transdermal groups. Plasma fentanyl clearance did not differ significantly between the groups. Plasma fentanyl concentrations decreased slowly after removal of the transdermal system.

TTS-fentanyl is a rate-controlled adhesive skin patch, which contains fentanyl in a sealed drug reservoir and is applied to a hair-free area of the skin on the upper chest. In this study it was designed to deliver fentanyl at a rate of 100 μg h^{-1}.

TTS-fentanyl was applied 2 h before induction of anaesthesia. Patients were allocated to one of two groups. Group 1 received fentanyl 100 μg i.v.; group 2 received 200 μg.

Anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with 0.5–2 % enflurane and 67 % nitrous oxide in oxygen. Neuromuscular blockade was achieved with vecuronium 0.01 mg kg^{-1} given at induction of anaesthesia, with repeat bolus doses as required. The lungs were ventilated mechanically and normocapnia maintained. Neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.2 mg. Fentanyl was given i.v. at induction according to the group allocated.

Venous blood samples were taken at 0.5, 1, 2, 4, 8, 12 and 24 h after the start of fentanyl adminis-

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tration. Further samples were taken after the bolus dose given on induction of anaesthesia (2.25, 2.5 and 3 h). After 24 h, when the TTS-fentanyl was removed, samples were taken at 4, 8, 12 and 24 h. Plasma was separated and stored at −20 °C until plasma fentanyl concentrations were measured by radioimmunoassay [13, 14].

Immediately after removal of the TTS-fentanyl, the patch was sealed with an impermeable plastic backing. The amount of fentanyl remaining in the system was analysed by high performance liquid chromatography. The total amount of fentanyl delivered to the patient was calculated by subtracting the measured residual fentanyl from the amount inserted at manufacture.

Pain relief following surgery was assessed by the nursing and medical staff. Morphine 2.5–10 mg i.m. was given if analgesia was unsatisfactory. No formal assessment of pain scores was made.

Rate of ventilation was recorded hourly. The study was discontinued if it decreased to less than 8 b.p.m.

The anaesthetic regimen used in this study was identical to that used in a control group of patients receiving fentanyl 100 $\mu g\ h^{-1}$ by i.v. infusion (group 3). The infusion was commenced 2 h before induction of anaesthesia and delivered by a Baxter Travenol Infusor [2]. All patients in this group received fentanyl 100 µg i.v. at induction of anaesthesia. Blood samples were taken at the same time intervals as the TTS groups during the infusion of fentanyl. Samples were then taken at 0.5, 1, 2 and 4 h after cessation of the infusion. Plasma was stored and analysed as described above.

Pharmacokinetic calculations

Plasma clearance and half-life were calculated for each patient from the plasma fentanyl concentrations. The area under the curve to infinity (AUC^{∞}) was calculated by the trapezoid method with extrapolation of the concentration–time curve to infinity. The elimination rate constant was calculated from the slope of the decrease in plasma fentanyl concentrations after removal of the transdermal system or infusion. The following equations were used:

$$Cl_P = \frac{Xd^{tot}}{AUC^{\infty}} \qquad (1)$$

$$T_{\frac{1}{2}} = \frac{\ln 2}{k} \qquad (2)$$

where Cl_P = plasma clearance; Xd^{tot} = total dose administered; AUC^{∞} = area under the concentration time–curve to infinity; k = rate constant; $T_{\frac{1}{2}}$ = plasma half-life.

Plasma fentanyl concentrations and pharmacokinetic values were compared using one-way analysis of variance and Student's *t* test.

RESULTS

There were no significant differences in age, weight, sex, duration of surgery and surgical procedure between the groups (table I).

Mean plasma fentanyl concentrations are shown in figure 1 and table II. Comparisons between groups were made from 4 h onwards. At 4 h, plasma fentanyl concentrations were significantly greater in group 3 when compared with group 1 ($P < 0.001$) and group 2 ($P < 0.05$). There was no significant difference between group 1 and 2. At 8 and 12 h there were no significant differences between the groups. At 24 h, concentrations in group 2 were significantly less than group 3 ($P < 0.001$) and group 1 ($P < 0.01$). There were no significant differences between the groups 4 h after fentanyl removal.

Plasma fentanyl concentrations decreased significantly 4 h after discontinuation of fentanyl in

TABLE I. *Details of patients and operations (mean ± SD). No significant differences between groups (analysis of variance and chi-square tests)*

	Age (yr)	Weight (kg)	Sex M/F	Duration of surgery (min)	Operation
Group 1 (n = 10)	49±12	70±10	6/4	105±40	9 Cholecystectomy 1 Gastric surgery
Group 2 (n = 9)	49±11	74±13	5/4	111±40	7 Cholecystectomy 2 Gastric surgery
Group 3 (n = 13)	49±14	64±14	4/9	100±30	9 Cholecystectomy 4 Gastric surgery

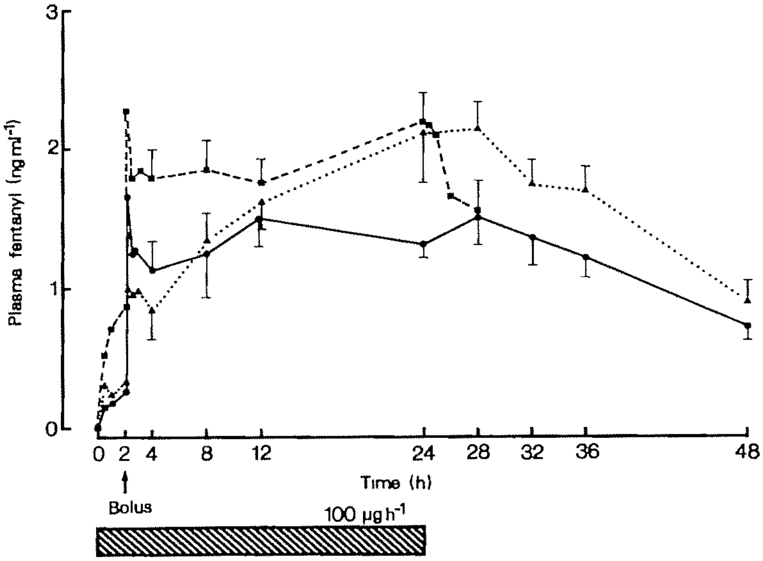

FIG. 1. Mean ± SEM plasma fentanyl concentrations in patients in group 1 (▲: transdermal fentanyl plus fentanyl 100 µg (Bolus) at induction of anaesthesia), group 2 (●: transdermal fentanyl plus fentanyl 200 µg (Bolus) at induction of anaesthesia) and group 3 (■: control; i.v. infusion of fentanyl 100 µg h^{-1} (cross-hatched bar) plus 100-µg Bolus).

TABLE II. *Plasma fentanyl concentrations (mean ± SEM). Groups compared by ANOVA from 4 h: *P < 0.05; ***P < 0.001 compared with group 3; ††P < 0.01 compared with group 2*

	Plasma fentanyl concentrations (ng ml⁻¹)		
Time (h)	Group 1 TTS-fentanyl 100-µg bolus	Group 2 TTS-fentanyl 200-µg bolus	Group 3 i.v. infusion 100-µg bolus
0.5	0	0	0.5±0.1
1	0	0	0.7±0.1
2	0.3±0.1	0.3±0.1	0.8±0.1
2.25	1.0±0.2	1.6±0.1	2.3±0.4
2.5	0.9±0.2	1.2±0.1	1.8±0.1
3	1.0±0.3	1.3±0.2	1.8±0.2
4	0.7±0.2***	1.1±0.2*	1.8±0.2
8	1.3±0.2	1.2±0.3	1.8±0.2
12	1.6±0.2	1.5±0.2	1.8±0.2
24	2.0±0.2††	1.3±0.1***	2.3±0.2
	Fentanyl discontinued at 24 h		
0.5	—	—	2.2±0.3
1	—	—	2.1±0.3
2	—	—	1.7±0.1
4	2.1±0.2	1.5±0.2	1.6±0.2
8	1.7±0.2	1.3±0.2	—
12	1.7±0.2	1.2±0.2	—
24	0.8±0.2	0.7±0.1	—

group 3 ($P < 0.01$, paired t test). There was a small increase in groups 1 and 2, but this was not statistically significant. The maximum individual increases in plasma fentanyl concentrations at this time were 116% (from 1.2 to 2.6 ng ml^{-1}) in group 1 and 92% (from 0.68 to 1.31 ng ml^{-1}) in group 2.

Plasma fentanyl concentrations decreased slowly in the TTS-fentanyl groups over 24 h, but exact comparison with the i.v. infusion group was not possible because blood samples were taken only up to 4 h after stopping fentanyl in this group. At 12 h, all patients in group 1 and 6 (66%) in group 2 had plasma fentanyl concentrations greater than 1 ng ml^{-1}. Twenty-four hour after the removal of TTS-fentanyl, two patients (20%) in group 1 and one (11%) in group 2 had plasma fentanyl concentrations greater than 1 ng ml^{-1}.

The mean calculated doses of fentanyl delivered by the TTS-fentanyl systems in 24 h are shown in table III. There were no significant differences between groups 1 and 2.

Pharmacokinetic values are shown in table IV. The mean plasma half-lives in groups 1 and 2 were 15.9 and 15.7 h, respectively. The mean plasma clearance was greater in group 2, but this was not statistically significant. Pharmacokinetic data for the i.v. group were not compared statistically with the TTS groups, as the final blood sample in the i.v. group was taken only 4 h after stopping the infusion.

Two patients from group 2 were withdrawn

TABLE III. *Total amount of fentanyl (mg) delivered by TTS systems in 24 h (mean ± SEM)*

	Total fentanyl (mg)
Group 1	2.25 ± 0.28
Group 2	2.33 ± 0.18

TABLE IV. *Calculated plasma fentanyl clearances, half-lives and AUC$^\infty$ (mean ± SEM). No significant differences between group 1 and 2. Group 3 not compared*

	Clearance (ml min^{-1})	Plasma half-life (h)	AUC$^\infty$ (ng min ml^{-1})
Group 1 ($n = 10$)	450 ± 59	15.9 ± 2.3	5715 ± 791
Group 2 ($n = 9$)	650 ± 70	15.7 ± 2.3	4379 ± 628
Group 3 ($n = 13$)	720 ± 70	8.5 ± 2.0	5412 ± 511

from the trial. In both patients, the ventilatory rate decreased to less than 8 b.p.m. during sleep. Plasma fentanyl concentrations at these times were 2.8 and 2.9 ng ml^{-1}. Both patients had received supplementary morphine 20 mg and 10 mg, respectively.

DISCUSSION

The range of plasma fentanyl concentrations associated with analgesia and acceptable respiratory function is 1–3 ng ml^{-1} [15–17]. Estimates of the half-life of fentanyl have varied [16], but it is clear that, after constant rate delivery, steady state would be achieved only after many hours. However a bolus of fentanyl 100 µg at induction of anaesthesia, combined with fentanyl 100 µg h^{-1} by continuous i.v. infusion, has produced steady-state concentrations rapidly and within the range 1–3 ng ml^{-1} in surgical patients [12].

In the present study, these data have been compared with two TTS groups in which fentanyl 100 µg and 200 µg boluses were given at induction of anaesthesia. With TTS-fentanyl and 100 µg bolus (group 1), concentrations did not differ significantly from the i.v. group between 8 and 24 h. At 4 h, however, only one patient had a plasma concentration greater than 1 ng ml^{-1}. With TTS-fentanyl and 200-µg bolus (group 2), five patients had concentrations greater than 1 ng ml^{-1} at 4 h. Plasma concentrations did not differ from group 3 at 8 and 12 h. However, concentrations were significantly lower than in the other groups at 24 h. There was no significant difference between the TTS-fentanyl groups in the total amount of fentanyl administered. Thus, lower mean plasma fentanyl concentrations at 24 h may be related to the greater plasma clearance in group 2, although this difference did not achieve statistical significance.

Four hours after discontinuation of the i.v. infusion, plasma fentanyl concentrations had decreased significantly. In both transdermal groups the mean concentrations increased, although not significantly. Two patients in this study showed a marked increase (92 % and 116 %) in plasma fentanyl concentrations after removal of the patch. This had no observable clinical effect on these patients. These data, combined with the delay in achieving therapeutic concentrations after application of the system, are compatible with a depot of fentanyl forming in the skin.

When the calculated pharmacokinetic values in the TTS-fentanyl groups are compared with those from other studies with i.v. fentanyl [15], the mean half-life of approximately 16 h is much greater than those found in these studies. Direct statistical comparison with group 3 in our study ($T_{\frac{1}{2}} = 8.5$ h) has not been made because of the short sampling time after stopping the infusion. Plasma fentanyl clearance in the transdermal groups did not differ markedly from that reported in other studies. It is likely that the prolonged plasma half-life of fentanyl in these patients is also a result of deposits of the drug remaining in the skin when the patch is removed.

This slow decline in plasma fentanyl concentration may be advantageous when the system is used for the relief of postoperative pain, but it should be borne in mind if the patch is removed because of side-effects from fentanyl.

Plasma fentanyl concentrations in the two patients withdrawn from the study (2.8 and 2.9 ng ml^{-1}) were both within the therapeutic range. Supplementary morphine had been given to both patients and this probably contributed to the respiratory depression (ventilatory rates < 8 b.p.m.).

The delivery of fentanyl by the transdermal route may be useful in the treatment of pain after surgery. If it is applied 2 h before surgery, combined with a bolus dose of 200 µg i.v. at induction of anaesthesia, steady-state fentanyl concentrations occur early in the postoperative period. Concentrations decline slowly after its removal.

ACKNOWLEDGEMENT

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PHARMACOKINETICS OF FENTANYL IN THE ELDERLY

M. A. SINGLETON, J. I. ROSEN AND D. M. FISHER

SUMMARY

The pharmacokinetics of fentanyl were determined in seven elderly (71–82 yr) and seven younger adults (18–41 yr) anaesthetized with thiopentone, nitrous oxide in oxygen and morphine. Fentanyl was administered as a 2-min i.v. infusion at doses of 15 μg kg⁻¹ for elderly patients and 20 μg kg⁻¹ for the younger patients. Plasma samples were obtained for 4 h and fentanyl concentrations determined by radioimmunoassay. Fentanyl concentration, per μg kg⁻¹ administered, was higher in elderly than in young patients at 2 min (7.73 ± 3.14 v. *4.54 ± 1.83 ng ml⁻¹ (mean ± SD), respectively) and at 4 min after the start of infusion (3.26 ± 1.44* v. *1.78 ± 0.72 ng ml⁻¹, respectively). Concentrations were similar at all other sampling times. Pharmacokinetic variables were determined by non-compartmental techniques. Total plasma clearance was similar for the two age groups. Volume of distribution at steady-state (V_D^{ss}) was smaller in elderly patients (1.36 ± 0.44* v. *2.27 ± 0.82 litre kg⁻¹). Despite age-related changes in V_D^{ss}, plasma fentanyl concentrations for the two groups were similar throughout the 4-h sampling period except immediately following administration. These results suggest that, if there are age-related differences in response to fentanyl, the likely pharmacokinetic explanation is the higher concentration of fentanyl in the elderly immediately following its administration.*

Elderly patients are believed to be more sensitive to the depressant effects of opioid drugs [1]. This increase in sensitivity may result from age-related changes in either the pharmacokinetics or the pharmacodynamics of the opioids. One possible explanation is that changes in organ function and structure (such as the increase in fat as a percentage of body weight or the decrease in hepatic blood flow) alter the distribution or elimination of such drugs. Another possibility is that changes in the central nervous system alter sensitivity to opioids. To determine whether the distribution or elimination of fentanyl is affected by age-related changes in organ function and structure, we compared the pharmacokinetics of fentanyl in elderly and young adults.

PATIENTS AND METHODS

After obtaining approval from our Committee on Human Research and informed consent from patients, we studied seven elderly (71–82 yr, three males) and seven younger adults (18–41 yr, four males), ASA class I or II. All patients were unpremedicated and undergoing elective non-abdominal surgery. Anaesthesia was induced with thiopentone 2–6 mg kg⁻¹ and maintained with 60 % nitrous oxide in oxygen. Pancuronium was administered and ventilation controlled to maintain end-tidal P_{CO_2} at 4.7–5.3 kPa. Nasopharyngeal temperature was maintained at 35–37 °C. After the induction of anaesthesia, fentanyl was administered as a 2-min i.v. infusion at doses of 15 μg kg⁻¹ for the elderly patients and 20 μg kg⁻¹ for the younger patients. A smaller dose of fentanyl was administered to the elderly patients because we were concerned that larger doses might not be tolerated clinically. Arterial plasma samples were obtained before infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min after the start of infusion. Plasma fentanyl concentrations were determined by radioimmunoassay [2, 3], sensitive to 0.5 ng ml⁻¹ [4] and having a coefficient of variation of 10 % at a concentration of 1.0 ng ml⁻¹. Non-compartmental techniques [5] were used to determine the following pharmacokinetic variables: elimination half-life ($T_{\frac{1}{2}}^{\beta}$); total plasma clearance (Cl); volume of distribution at steady-state (V_D^{ss});

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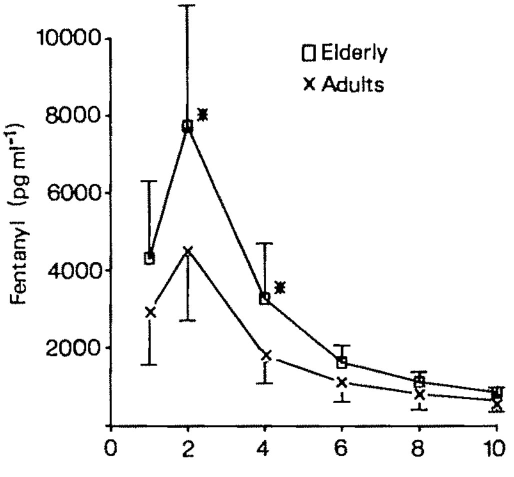

FIG. 1. Expanded plot of concentration (mean, SD) of fentanyl per μg kg⁻¹ administered against the first 10 min of time, for elderly and young adults. Fentanyl concentrations are higher in elderly subjects at 2 and 4 min after the beginning of the 2-min infusion.

mean residence time (Vd^{ss}/Cl). In addition, for each patient, we calculated the plasma concentration of fentanyl per μg kg⁻¹ administered at each sampling time. Mean values for the two age groups were compared using Student's *t* test for unpaired data [6]; $P < 0.05$ was considered significant.

TABLE I. *Pharmacokinetic data for fentanyl (mean ± SD). * Significantly different from young adults* ($P < 0.05$) *by Student's* t *test for unpaired data.*

	Young adults ($n = 7$)	Elderly ($n = 7$)
Dose (μg kg⁻¹)	20.7 ± 1.3	15.5 ± 0.7
$T_{\frac{1}{2}}{}^{\beta}$ (min)	133.0 ± 47.0	103.0 ± 52.0
Cl (ml kg⁻¹ min⁻¹)	13.9 ± 3.0	13.1 ± 4.1
Mean residence time (min)	165.0 ± 58.0	114.0 ± 56.0
Vd^{ss} (litre kg⁻¹)	2.27 ± 0.82	1.36 ± 0.44*

RESULTS

Fentanyl concentration per μg kg⁻¹ administered was higher in the elderly than in the younger patients at 2 min (7.73 ± 3.14 *v.* 4.54 ± 1.83 ng ml⁻¹ (mean ± SD), respectively) and at 4 min after the start of infusion (3.26 ± 1.44 *v.* 1.78 ± 0.72 ng ml⁻¹, respectively) (fig. 1). Concentrations at all other sampling times were similar for both age groups (figs 1, 2).

Elderly patients had a smaller volume of distribution at steady-state compared with young patients (table I).

There were no differences in $T_{\frac{1}{2}}{}^{\beta}$, Cl or mean residence time.

DISCUSSION

If the elderly are more sensitive to the depressant effects of opioids [1], age-related changes in the pharmacokinetics or pharmacodynamics of such

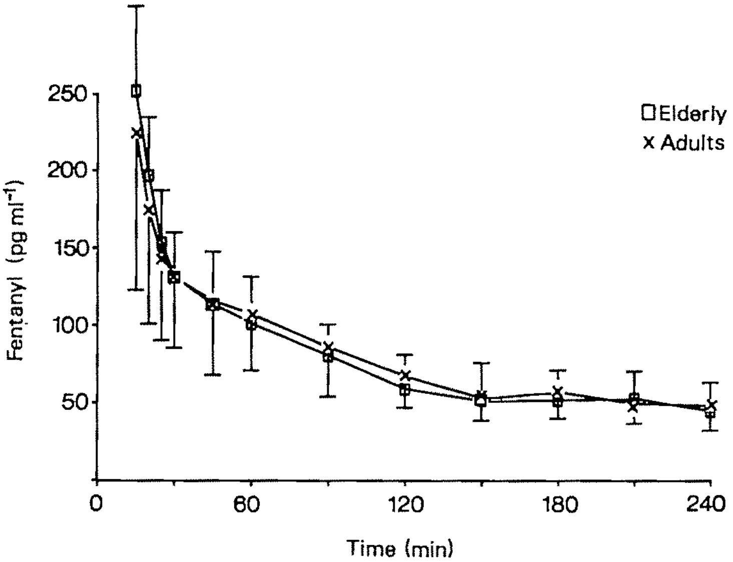

FIG. 2. Concentration (mean, SD) of fentanyl per μg kg⁻¹ administered plotted against time for elderly and young adults.

drugs could be the explanation. In this study, we found that the pharmacokinetics of fentanyl were similar for elderly and young patients, except for a smaller volume of distribution at steady-state in the elderly. In addition, following the administration of weight-normalized doses, plasma fentanyl concentrations were similar at all times except in the period immediately following administration. Consequently, during recovery from anaesthesia; that is 120–240 min after fentanyl administration, plasma fentanyl concentrations were similar in both groups.

Physiological changes associated with ageing would be expected to influence the metabolism and distribution of fentanyl. For example, ageing decreases liver blood flow [7]. Since most of the fentanyl entering the hepatic circulation is metabolized, this decrease in liver blood flow should decrease the clearance of fentanyl. However, we found no age-related decrease in *Cl*. Our finding is similar to that for lignocaine [8], another drug highly extracted by the liver, and may reflect our selection of healthy elderly subjects.

Another age-related change is a decrease in lean body mass and an increase in fat as a percentage of body weight [9]. For lipophilic drugs such as fentanyl, this should increase the volume of distribution at steady-state. In contrast, we found that $V\text{D}^{ss}$ for fentanyl was smaller in the elderly group. The $V\text{D}^{ss}$ for another lipophilic drug, thiopentone, is similar in young and elderly subjects [10]. Thus, ageing does not necessarily increase the $V\text{D}^{ss}$ of lipophilic drugs.

Ageing is also associated with the decrease in the volume of extracellular fluid as well as a decrease in blood flow to organs in the vessel-rich group [10]. These factors may limit the distribution of fentanyl from blood, resulting in a higher initial plasma concentration, and would explain the higher concentration of fentanyl observed in our elderly patients immediately after administration. This higher initial concentration has also been observed with thiopentone [10] and may explain the greater response of the elderly to weight-normalized doses of that drug [10]. In support of this, Homer and Stanski [10] have demonstrated that the steady-state plasma concentrations of thiopentone that produce the same degree of electroencephalographic depression are similar in young and elderly subjects. Thus, the greater response of the elderly to weight-normalized doses of thiopentone is the result of pharmacokinetic changes; that is, a higher initial plasma concentration and, because thiopentone enters the brain rapidly, presumably a higher initial brain concentration.

Fentanyl also enters the brain rapidly [11]. Consequently, higher peak plasma concentrations of fentanyl in elderly patients may result in a greater peak response, such as depression of ventilation. Within 10 min of administration of weight-normalized doses, plasma fentanyl concentrations were similar in elderly and young patients. Thus, pharmacokinetic differences could explain only differences in peak response, and not differences occurring 1–4 h after administration.

Ageing may also produce pharmacodynamic changes that explain the more profound response of elderly patients to opioids. These pharmacodynamic changes may involve either differences in drug concentrations in the brain (for example, if there were less protein binding of fentanyl in the elderly) or differences in the sensitivity of the brain. Changes in the ventilatory response with ageing have been investigated in two studies. Arunsalam and colleagues [12] obtained ventilatory measurements before and after the i.v. administration of morphine 10 mg/70 kg, to young and elderly subjects. The decreases in minute ventilation and ventilatory frequency and the increase in end-tidal $P\text{CO}_2$ were comparable for both. However, more than half of the elderly subjects had significant episodes of apnoea or periodic breathing. In contrast, apnoea or periodic breathing occurred in fewer than 25% of the young subjects and with a lower frequency. These results suggest that, for a comparable pharmacodynamic endpoint (increase in $P\text{CO}_2$ or decrease in minute ventilation), elderly subjects differ from young subjects in ventilatory pattern in response to morphine.

Peterson and co-workers [13] found that ventilatory responses to hyperoxic hypercapnia and isocapnic hypoxia were blunted approximately 50% in elderly subjects. These decreases in ventilatory response were proportional to an age-related decrease in occlusion pressure response (the inspiratory pressure generated 100 ms after airway occlusion). Peterson and co-workers [13] concluded that the difference in the pattern of ventilation resulted from age-related changes in neuromuscular, rather than central nervous system, function.

In combination, these two studies suggest that the ventilatory response of the elderly differs both in the presence [12] and absence [13] of opioids.

Our findings differ from those of Bentley and colleagues [14] who compared the pharmacokinetics of fentanyl in four elderly women (mean age 67 yr; range 61–73 yr) and five young women (mean age 36 yr; range 29–49 yr). They found that the volume of distribution was similar for elderly and young patients (4.9 ± 0.5 and 5.9 ± 0.8 litre kg^{-1} (mean ± SEM), respectively) and that *Cl* was decreased markedly in the elderly patients (4.0 ± 0.6 *v.* 15.4 ± 1.6 ml kg^{-1} min^{-1}). They obtained samples for 7 h (in contrast to 4 h in our study), and determined fentanyl concentrations by gas chromatography. Their anaesthetic technique (nitrous oxide, thiopentone and controlled ventilation) was similar to ours. Two differences in study design may explain the difference in results. First, Bentley and colleagues [14] did not measure $P\mathrm{CO}_2$. This is important because hyperventilation, and the attendant hypocarbia, are known to decrease clearance of fentanyl [15]. Second, all of their subjects (and none of ours) underwent abdominal surgery, which produces a significant decrease in hepatic blood flow [16] that may alter the clearance of fentanyl.

In summary, we found that the clearance of fentanyl was similar in elderly and younger patients, and $V\mathrm{D}^{ss}$ smaller in elderly patients. Plasma concentration of fentanyl was higher in the elderly patients immediately after administration, but similar for the two age groups during the subsequent 4 h. Our results suggest that if the effects of fentanyl are more pronounced in elderly subjects, the likely pharmacokinetic explanation is the higher initial concentration.

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COMPARATIVE PLASMA CONCENTRATION PROFILES AFTER I.V., I.M. AND RECTAL ADMINISTRATION OF PETHIDINE IN CHILDREN

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A. B. LARSEN AND E. F. HVIDBERG

SUMMARY

Plasma concentration–time curves of pethidine and norpethidine were studied in 25 children allocated after operation to three groups to receive pethidine 1 mg kg^{-1} i.v., i.m. or rectally. Peak concentrations occurred after 5 ± 1, 10 ± 2, and 60 ± 10 min, respectively, while the maximum concentrations amounted to 2800 ± 462, 1609 ± 367 and 531 ± 179 nmol litre^{-1}, respectively. The area under the curve (0–240 min) was similarly reduced in the group with rectal administration (P < 0.05). Compared with the i.v. data, approximately 40% systemic availability occurred after rectal application, although considerable individual variation was noted. In one child very high plasma concentrations were observed after rectal administration, possibly as a result of redistribution/recirculation phenomena. The average results are similar to those obtained when other opioids are given rectally.

The systemic bioavailability of pethidine is approx. 50% after oral administration because of considerable first-pass metabolism in the liver [1]. Several metabolites are formed including norpethidine, which has some analgesic activity [2–4].

Rectal administration of drugs is well established [5–8] and may be advantageous, especially in children, to avoid painful injections [9]. Furthermore, presystemic elimination may be reduced [8].

The aim of the present study in children was to describe the time–concentration profiles of both pethidine and norpethidine following rectal administration of pethidine, compared with those obtained after parenteral application.

PATIENTS AND METHODS

Twenty-five otherwise healthy children (age 7–13 yr, mean 10 yr) undergoing elective surgery (predominantly for undescended testis) were investigated. The study was approved by the local Ethics Committee and informed consent was obtained from both child and parents.

The general design of the investigation was an open, randomized study in three parallel groups. All patients received pethidine 1 mg kg^{-1} i.v., i.m. or rectally. One hour before anaesthesia diazepam 0.2 mg kg^{-1} was given orally as premedication. Anaesthesia was induced and maintained with halothane and 50% nitrous oxide in oxygen using a face-mask. The appropriate dose of pethidine (pethidine hydrochloride 10 mg ml^{-1} in 0.9% sodium chloride, pH 7.5 (DAK, Copenhagen)) was given either parenterally i.v., or i.m. in the thigh. Rectal pethidine was applied with a syringe supplied with a blunt plastic applicator introduced 2–3 cm into the rectum.

The plasma concentrations of pethidine and its main metabolite norpethidine were analysed in blood samples drawn before and at 5, 10, 15, 40, 60, 90, 120, 180 and 240 min after the adminis-

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tration of pethidine. Three millilitre of blood was collected into heparinized test tubes from an i.v. cannula (sited in the arm opposite to that used for i.v. injection) and centrifuged. Plasma was removed, frozen immediately and stored at −20 °C until analysed by gas chromatography/mass spectrometry in the positive chemical ionization mode. Plasma to which the internal standard, pentadeuterated pethidine, was added was made alkaline and extracted with tert-butylmethylether. The organic phase was evaporated and redissolved in ethanol. One microlitre was injected into a wide-bore capillary column HP-17 cross-linked 10 m × 0.53 mm × 2.0 µm film thickness. Column temperature was 180 °C and injector heated to 250 °C. Methane 4 ml min^{-1} was used as carrier and reactant gas. Pethidine, norpethidine and internal standard were monitored at (mass to charge) = 248.2, 234.2 and 253.3, respectively. Coefficient of variation (CV) on duplicates was 3% (mean concentration = pethidine 1039 nmol $litre^{-1}$) and 18.6% (mean concentration = norpethidine 77 nmol $litre^{-1}$). The latter CV reflects the fact that it was not possible to synthesize an appropriate internal standard. Limit of detection was 200 fmol for injected amount of pethidine and 1 pmol for injected amount of norpethidine. Further details of the assay will be published elsewhere.

Because of ethical problems and anticipated difficulties in co-operation from the children, the blood sampling period was limited to 240 min. A correct β-phase could, therefore, not be obtained and accordingly an elimination constant (or $T_{\frac{1}{2}}$) could not be calculated. Based on the resulting concentration–time curves of both components in all patients, the following variables were determined: maximum plasma concentration (C^{max}); time to peak concentration (T^{max}); the area under the curve AUC_{240} calculated by the trapezoidal rule method.

Statistical analyses were by Student's *t* test for paired and unpaired observations after analysis of variance (*F* test). A 95% level of significance was chosen. All results are given as mean ± one standard deviation (SD).

As pethidine is administered in milligram doses and pethidine and norpethidine are presented in molecular units, the following conversion factors may be used: Pethidine: nmol $litre^{-1} \times 0.247$ = µg $litre^{-1}$; µg $litre^{-1} \times 4.04$ = nmol $litre^{-1}$. Norpethidine: nmol $litre^{-1} \times 0.233$ = µg $litre^{-1}$; µg $litre^{-1} \times 4.29$ = nmol $litre^{-1}$.

RESULTS

There were no significant differences in patient characteristics between groups (table I).

While C^{max} of 2800 ± 462 nmol $litre^{-1}$ (i.v.) (fig. 1) and 1609 ± 367 nmol $litre^{-1}$ (i.m.) (fig. 2) occurred after 5 ± 1 min and 10 ± 2 min,

TABLE I. *Patient characteristics and pharmacokinetic results (mean (SD)) after different routes of administration of pethidine 1 mg* kg^{-1}. **P < 0.05 compared with i.v. and i.m. administration*

	Route of administration		
	I.v. ($n = 10$)	I.m. ($n = 6$)	Rectal ($n = 9$)
Age (yr)	9.6 (2.6)	10.2 (2.8)	9.6 (2.6)
Weight (kg)	32.9 (7.6)	30.3 (5.8)	31.8 (8.9)
Pethidine			
Dose (mg)	33 (8)	30 (6)	32 (9)
Applied volume (ml)	3.3 (0.8)	3.0 (0.6)	3.2 (0.9)
Auc_{240} (nmol $litre^{-1}$ h)	3769 (96)	3951 (110)	1327 (667)*
C^{max} (nmol $litre^{-1}$)	2800 (462)	1609 (367)	531 (179)*
T^{max} (min)	5 (1)	10 (2)	60 (10)*
Norpethidine			
C^{max} (nmol $litre^{-1}$)	137 (60)	103 (32)	135 (65)
T^{max} (min)	90 (17)	120 (23)	180 (25)

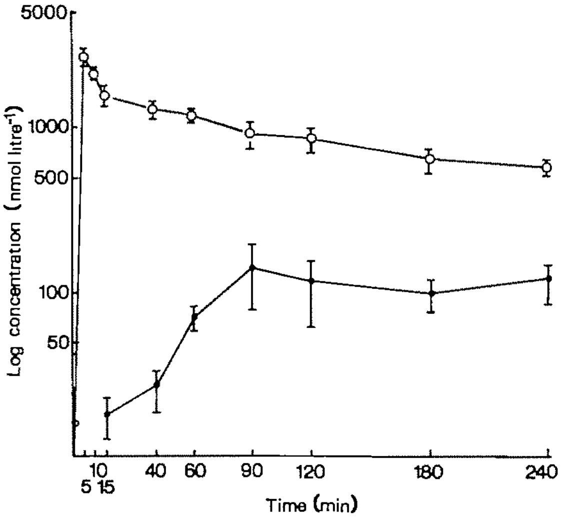

FIG. 1. Semilogarithmic plot of pethidine (○) and norpethidine (●) concentrations against time in 10 patients receiving pethidine i.v.

respectively, C^{max} of only 531 ± 179 nmol litre^{-1} (fig. 3) occurred 60 ± 10 min after the rectal administration (table I). The mean peak plasma concentration of norpethidine was reached after 90 ± 17 min (i.v.) 120 ± 23 min (i.m.) and 180 ± 25 min (rectal) (table I). If the mean AUC_{240} value of the i.v. group is used as reference the average systemic bioavailability after rectal application of pethidine was approximately 40 % with a range of variability in the nine patients of 32–81 %.

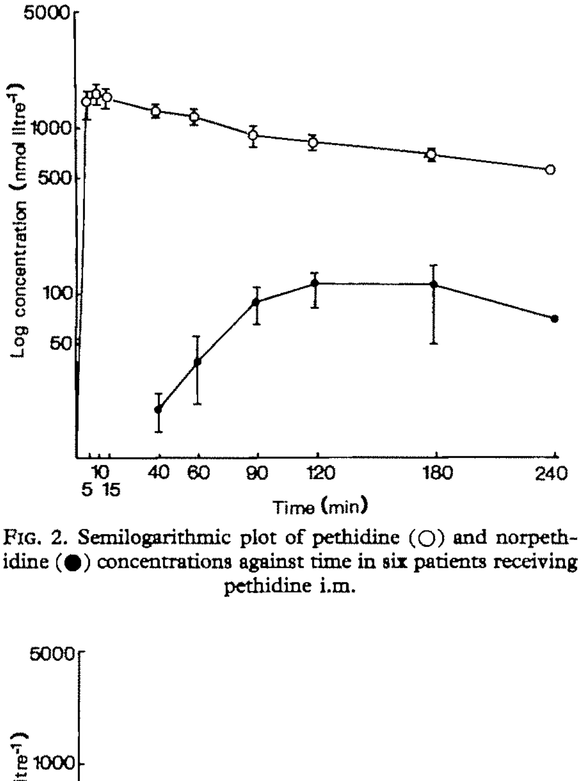

FIG. 2. Semilogarithmic plot of pethidine (○) and norpethidine (●) concentrations against time in six patients receiving pethidine i.m.

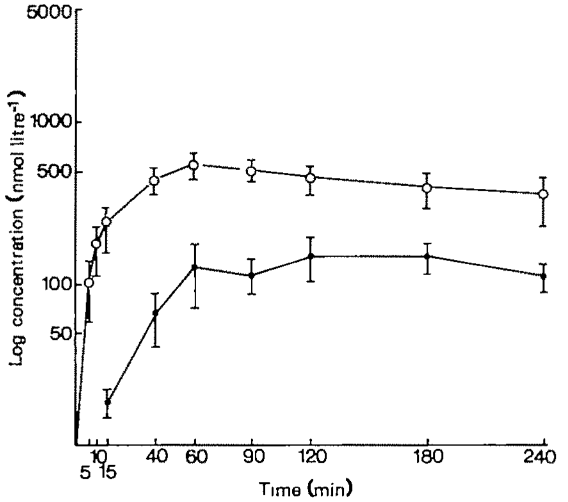

FIG. 3. Semilogarithmic plot of pethidine (○) and norpethidine (●) concentrations against time in nine patients receiving pethidine rectally.

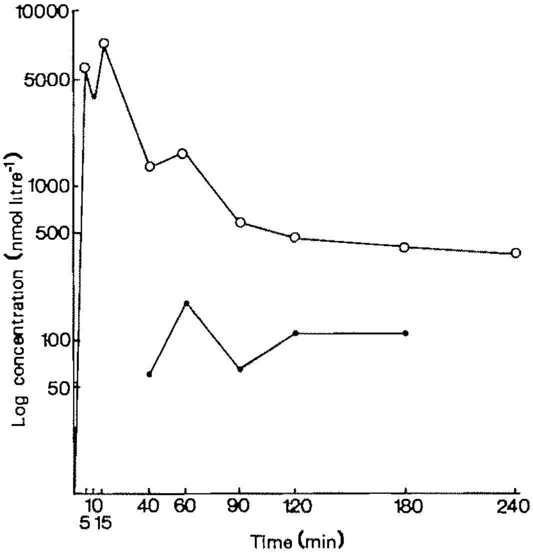

FIG. 4. Pethidine (○) and norpethidine (●) concentration–time profile for one patient with an unusually high plasma concentration after rectal administration of pethidine.

The pethidine plasma concentration–time profile of one child in the rectal group differed in demonstrating three peaks (fig. 4) and concentrations far exceeding the i.v. results. However, after 90 min the values were comparable to those of the rest of the group. At that time the norpethidine concentration was also similar to the average value in the group.

DISCUSSION

When given orally, approx. 50 % of pethidine becomes systemically available because of presystemic metabolism [1]. While i.v. and, to some extent, i.m. routes provide the most predictable results in this respect, drugs administered via the rectum may also avoid presystemic metabolism [8, 10]. However, the time to reach peak plasma concentrations in the present study reveals that the rate of absorption of pethidine was grossly delayed after rectal application compared with the i.m. or i.v. routes. Furthermore, both the maximum concentrations and the AUC_{240} demonstrate that the amount of pethidine (in the relevant period) available for analgesic action after rectal administration was approx. 40 % of the amount available after parenteral administration. Poor absorption from the rectum is clearly the main reason for this discrepancy, although a minor contribution may be some degree of presystemic metabolism. The faster appearance of norpethidine in the rectal group (figs 1–3) may support this, although no data demonstrate it directly. Difficulties in placing the drug correctly in the short rectum of the child, adsorption by faecal content and loss of the drug via the anus are probably the main reasons for the delayed or incomplete absorption of the drug.

Rectal administration of other opioids has been investigated, for example morphine in adults [11, 12] and children [13], pentazocine [14, 15], ketobemidone [16] and oxymorphone [17]. In all instances, the bioavailability was similar to that of pethidine given rectally in the present study.

Although it was not possible to determine the elimination constant, the average curves of the i.v. and i.m. groups (figs 1, 2) suggest half-lives (3–4 h) similar to those quoted elsewhere [1, 18]. This is not the case for the rectal group, suggesting that the drug was still being absorbed at these times after rectal administration (fig. 3).

The very high plasma concentration of pethidine in one child following rectal administration (fig. 4) may have been caused by redistribution of blood from the visceral to the peripheral pool following induction of anaesthesia. However, abnormal vasculature of the rectum or deficiency of pethidine carboxylesterase in the liver cannot be excluded. The double peaks (fig. 4) are seen not uncommonly with opioids and an explanation may also depend on entero–hepatic recirculation.

The results of the present study in children demonstrate slow absorption rate and low bioavailability following rectal administration of pethidine. The latter problem may be overcome by increasing the dose, but the large individual variability of the plasma concentration–time profiles mitigates against this manoeuvre in this group.

The i.m. route of administration is also thought to be associated with erratic absorption, but this was only partly confirmed in the present study.

In conclusion, we recommend that the parenteral route of administration, preferably i.v., should be used for pethidine in the postoperative phase rather than the rectal route.

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COMPARISON OF EXTRADURAL BUPRENORPHINE AND EXTRADURAL MORPHINE AFTER CAESAREAN SECTION

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SUMMARY

Fifty-seven women received extradural morphine 3 mg, buprenorphine 0.18 mg or buprenorphine 0.09 mg after elective Caesarean section carried out under extradural bupivacaine. Supplementary sublingual buprenorphine was available on demand. Ten-centimetre visual analogue pain scores were completed regularly; emesis, pruritis and urinary retention were recorded for 24 h. Patients who received buprenorphine 0.09 mg had more pain, and required more supplementary analgesia, than those who received morphine 3 mg. Pain scores and analgesic requirements after buprenorphine 0.18 mg were not significantly different from either of the other two groups. Emesis was not significantly different in the three groups. More itching occurred after morphine 3 mg and buprenorphine 0.18 mg than after buprenorphine 0.09 mg; pruritis of the face, legs and perineum was more common after morphine than buprenorphine. Twenty-eight percent of patients without a urinary catheter developed retention of urine. Seventy-five to 84% of patients were satisfied with analgesia during the first day after operation. Analgesia and adverse effects were similar when morphine 3 mg or buprenorphine 0.18 mg was given extradurally after Caesarean section.

The extradural administration of opioids has been used increasingly in the management of postoperative pain since Behar and colleagues [1] first used extradural morphine 2 mg in the management of chronic pain. Larger doses of morphine became popular for extradural use until, by 1981, 10 mg was commonly given [2]. Although the extradural administration of these doses of morphine resulted in analgesia, respiratory depression was an unpredictable problem [3]. In 1982, rostral spread of extradural morphine 10 mg in cerebrospinal fluid, was confirmed by Bromage and colleagues [4].

Extradural morphine 4–8 mg provided 24–36 h of analgesia following Caesarean section, but adverse effects occurred after the use of larger doses [5–7]. It was postulated that a decrease in the dose of morphine (to 2–4 mg) would decrease the risk of respiratory depression [8]. However, extradural morphine 2 mg did not produce sufficient pain relief following Caesarean section [9]. Therefore, since Hanson, Hanson and Matousek [10] found extradural morphine 3 mg to be effective, this dose was used in the present study.

The effect of extradural opioids is dependent on the balance between direct dural transfer, fat deposition and systemic absorption. It was suggested that the use of lipid soluble drugs would reduce the risk of respiratory depression, as these entered neural tissue rather than remaining in the cerebrospinal fluid. However, when the extradural route is used, higher doses of lipid soluble agents were required to compensate for deposition in fat and systemic absorption [11].

Buprenorphine is highly lipid soluble, has potent intrinsic activity and binds strongly to the receptors [12]. As buprenorphine has such a high affinity for the mu receptor, it has been suggested that it may displace morphine and antagonize analgesia. However, there is no evidence that this occurs in the clinical situation. Buprenorphine

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0.1 mg was suggested as the optimum extradural dose for the relief of postoperative pain [13]. Therefore, the present study compared the effects of the extradural administration of buprenorphine 0.09 mg with morphine 3 mg—doses which were considered to be equipotent on i.m. administration [14]. Since it has been suggested that extradural dose requirements for buprenorphine are similar to i.v. ones because of the high lipid solubility of the drug [15,16], a larger dose of buprenorphine, 0.18 mg, was also studied.

PATIENTS AND METHODS

Fifty-seven women due to undergo elective Caesarean section under extradural analgesia were included in the study, which was approved by the Hospital Ethical Committee. Patients were graded ASA I or II; none had received analgesics for 24 h before surgery and all gave informed consent. Lower segment Caesarean section was performed under standardized extradural anaesthesia using 0.5 % plain bupivacaine 20–25 ml.

After surgery the patients were moved to the recovery room where they received the extradural opioid immediately, in a double-blind randomized manner. Preservative-free morphine 3 mg, buprenorphine 0.18 mg or buprenorphine 0.09 mg in a volume of 15 ml was given via the extradural catheter, which was subsequently removed. According to the policy of the obstetrician, the urinary catheter was left *in situ* overnight in 32 patients and removed in the remaining 25. Once they had recovered adequately, patients returned to the post-natal ward for observation.

After 1 h, analgesia was available on demand as sublingual buprenorphine (0.2 mg if < 60 kg; 0.4 mg if > 60 mg); the timing and number of doses required in the first 24 h were noted. A 10-cm visual analogue pain score was completed at 1, 2, 4, 6, 8, 10 and 24 h after extradural opioid injection. The visual analogue scores were interpreted as follows: 0–3.0 cm = no pain or mild pain, 3.1–6.6 cm = moderate pain and 6.7–10 cm = severe pain. Ventilatory rate was recorded hourly for 12 h. The occurrence of emesis, pruritis or urinary difficulty was noted. If necessary, emesis was treated with prochlorperazine and pruritis with naloxone. On the day after surgery, patients were asked to assess their satisfaction with the postoperative analgesia.

Parametric data were analysed using one-way analysis of variance for independent samples, followed by Scheffé's *S* test (if required). Non-parametric data (including pain scores) were analysed using Kruskal–Wallis one-way analysis of variance by ranks, Mann–Whitney *U*, Chi Square (partitioned, if necessary) and Fisher Exact Probability tests.

RESULTS

Nineteen patients received morphine 3 mg, 20 received buprenorphine 0.18 mg and 18 received buprenorphine 0.09 mg. There were no significant differences between the groups for age or weight (table I). The volume of 0.5 % bupivacaine used and the level of extradural block were similar in the three groups (using parametric and non-parametric analyses of variance, respectively).

During the first 2 h, 78 % of the patients in the morphine group, 85 % in the buprenorphine 0.18 mg and 94 % in the buprenorphine 0.09 mg group had no pain or mild pain. Thereafter, patients receiving morphine 3 mg or buprenorphine 0.18 mg had less pain than those in the buprenorphine 0.09 mg group at each time (fig. 1). At 6 h there was an increase in pain in all three groups: 32 % of the patients receiving morphine 3 mg, 40 % of those receiving buprenorphine 0.18 mg and 60 % of those receiving buprenorphine 0.09 mg had moderate pain. However, the only statistically significant difference in pain scores was at 8 h after extradural opioid administration, when patients receiving buprenorphine 0.09 mg had more pain than those receiving morphine 3 mg ($P < 0.05$) (fig. 1). The remaining percentage of patients who scored severe pain at any time in any group was never more than 15 %. Although there were no significant differences in the pain pattern in the three groups, there was a trend for pain to begin earlier in the buprenorphine 0.09 mg group and peak earlier in the buprenorphine 0.18 mg group (table II).

Patients receiving buprenorphine 0.09 mg required more sublingual buprenorphine than those receiving morphine ($P < 0.05$). The buprenor-

TABLE I. *Mean (SD) age and weight of patients. No significant difference between groups using analysis of variance for independent samples*

	Age (yr)	Weight (kg)
Morphine 3 mg (n = 19)	27.1 (5.2)	68.0 (12.6)
Buprenorphine 0.18 mg (n = 20)	28.5 (5.2)	70.5 (12.2)
Buprenorphine 0.09 mg (n = 18)	28.1 (4.8)	72.4 (14.8)

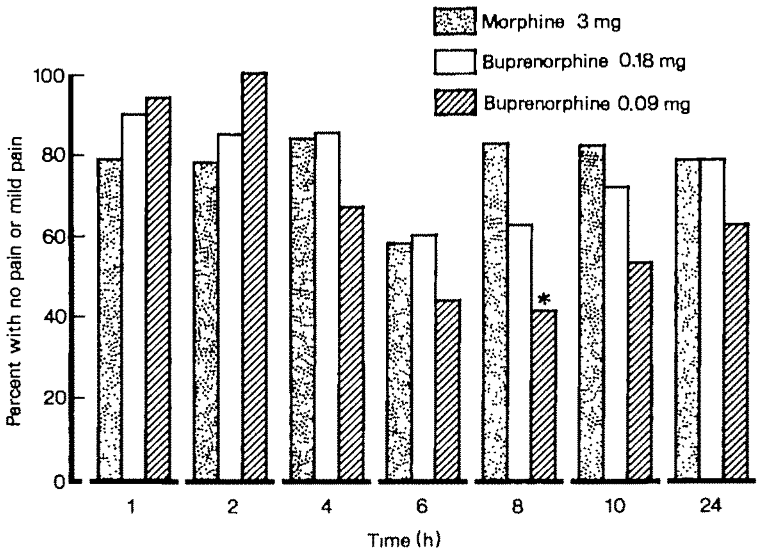

FIG. 1. Percent of patients in each group, at each time, with no pain or mild pain (visual analogue pain score of 0–3.3 cm). Significant difference between the groups at 8 h using Kruskal–Wallis analysis of variance ($H = 6.0$): *less than morphine using Mann–Whitney U test ($U = 101$, $P < 0.05$).

TABLE II. *Median (range) time to start of pain and peak pain scores. No significant difference between groups using Kruskal–Wallis analysis of variance*

	Time (h)	
	Start of pain	Peak pain
Morphine 3 mg ($n = 19$)	3.8 (1–10)	8.3 (1–24)
Buprenorphine 0.18 mg ($n = 20$)	3.6 (1–6)	6.5 (1–8)
Buprenorphine 0.09 mg ($n = 18$)	2.2 (1–10)	7.8 (1–24)

TABLE III. *Median (range) number of doses of sublingual buprenorphine during first 24 h and median (range) time, since extradural opioid, to request first dose of supplementary analgesia. Significant difference between the groups using Kruskal–Wallis analysis of variance* ($H = 7.56$): **more than morphine 3 mg using Mann–Whitney* U *test* ($U = 97$, $P < 0.05$)

	Number of doses	Time to first analgesia (h)
Morphine 3 mg ($n = 19$)	1.8 (0–5)	6.5 (2–35)
Buprenorphine 0.18 mg ($n = 20$)	2.9 (1–6)	5.8 (1–21)
Buprenorphine 0.09 mg ($n = 18$)	3.5 (1–6)*	5.0 (1–12)

phine 0.18 mg group fell between the other two groups, but was not significantly different from either (table III). There was no significant difference between the groups in the time to request the first dose of supplementary analgesia (table III).

A ventilatory rate of less than 10 b.p.m. was not recorded in any patient. Emesis was not significantly different in the three groups; however, there was a trend towards more nausea and vomiting with morphine and the larger dose of buprenorphine (table IV). When patients were questioned about pruritis, patients in the morphine and the larger dose buprenorphine groups complained of itch more than those in the lower dose buprenorphine group ($P < 0.05$) (table IV). However, only two patients in the morphine group and one in the higher dose buprenorphine group complained spontaneously of itching. Only one patient required naloxone for the treatment of pruritis; she had received buprenorphine 0.18 mg. There was more itching of the face ($P < 0.05$), legs and perineum ($P < 0.01$) after mor-

TABLE IV. *Incidence of emesis and pruritis. Significant difference between groups using Chi-square* ($\chi^2 = 9.15$): **more than buprenorphine 0.09 mg* ($P < 0.05$)

	Emesis (%)	Pruritis (%)
Morphine 3 mg ($n = 19$)	42	63*
Buprenorphine 0.18 mg ($n = 20$)	40	55*
Buprenorphine 0.09 mg ($n = 18$)	17	17

TABLE V. *Distribution of pruritis. Significant differences between the groups using Fisher Exact Test*: $^*P < 0.05$; $^{**}P < 0.01$

	Pruritis at each site (%)		
	Face	Legs/ perineum	Thorax/ abdomen
Morphine 3 mg ($n = 12$)	50*	75**	75
Buprenorphine 0.18 mg ($n = 11$)	9	18	91

phine than after buprenorphine; itching of the thorax and abdomen was similar in both groups (table V). Retention of urine occurred in seven of the 25 patients who were not catheterized, with a similar distribution between the groups.

There was no significant difference between the groups in the subjective assessment of satisfaction with postoperative analgesia; 84% of patients who received morphine 3 mg, 75% who received buprenorphine 0.18 mg and 78% who had buprenorphine 0.09 mg were satisfied or very satisfied.

DISCUSSION

Visual analogue pain scores must be treated as ordinal scales and analysed non-parametrically [17]. The difficulty in interpretation of visual analogue scores was shown in the present study by the inability to demonstrate statistically significant differences in pain scores at more than one time point. The similarity in pain scores in the three groups may also have been caused by the availability of supplementary analgesia. This allowed patients to regulate their pain scores which, therefore, did not exactly reflect the efficacy of the extradural opioid.

Most patients experienced minimal pain during the first 2 h after the extradural opioid, probably because of the persistent effect of the bupivacaine. At 4 h, the buprenorphine 0.09 mg group began to have more pain than the other two groups, a trend which persisted throughout the 24 h of assessment. Increased pain at 6 h in all groups may have reflected mobilization after recovery from motor blockade. The occurrence of pain was indirectly deduced from the amount of additional analgesia requested. The superiority of morphine 3 mg compared with buprenorphine 0.09 mg, suggested by the pain scores, was confirmed by the greater requirement for supplementary analgesia in the buprenorphine 0.09 mg group. The delayed peak pain scores seen in these patients may have reflected earlier administration of supplements of sublingual buprenorphine.

Therefore, morphine 3 mg and buprenorphine 0.09 mg, which were regarded as equipotent when given systemically, were not equally efficient when given extradurally. This finding contrasts with previous work, when similar quality and duration of analgesia were reported when systemically equivalent extradural doses of buprenorphine 0.15 mg and morphine 5 mg were compared [18]. Similarly, comparable analgesia was also seen when buprenorphine 0.06 mg or morphine 2 mg was given extradurally after abdominal surgery [19]. Therefore, the present study supports the concept that, in order to achieve satisfactory analgesia, extradural buprenorphine should be given in a dose similar to that used systemically [20]. A higher dose of the lipid soluble buprenorphine may be needed to compensate for systemic uptake and deposition in fat; it was suggested that, using the extradural route, buprenorphine 0.23 mg was equipotent with morphine 3 mg [16].

In the present study, there was substantial individual variation in the duration of action of the extradural opioid, which was inferred from the time taken to request the first dose of supplementary analgesia. As the duration of action of 5.0–6.5 h was rather shorter than previously reported, it may have been preferable to have left the extradural catheter *in situ* and to have administered further extradural opioid on demand. However, this would have increased staffing requirements and may have resulted in cumulation.

Extradural buprenorphine was recommended to produce analgesia with a "total lack of side effects" [18]. In the present study, a similar and rather high frequency of emesis and pruritis occurred with morphine 3 mg and buprenorphine 0.18 mg. However, the frequency of adverse effects was low after buprenorphine 0.09 mg, as suggested by Cahill and colleagues [19] using 0.06 mg. The presence of itching was easy to illicit, but most women did not complain spontaneously, and only one patient requested treatment. The concept that the more lipid soluble drugs do not spread rostrally is supported by the segmental distribution of pruritis after buprenorphine. A similar pattern of itching was seen following extradural fentanyl after Caesarean section [21]. Therefore, the risk of respiratory problems may be reduced after extradural buprenorphine compared with morphine. However, after low-dose lumbar extradural morphine, the risk of respiratory depression was minimal in fit women [3]. It is difficult to interpret the frequency of retention of urine, as some patients were catheterized and others were not. However, a 28 % frequency in women who were not catheterized suggests that it may be preferable to leave a urinary catheter *in situ* for 12 h after the use of extradural opioids.

In conclusion, as buprenorphine is not a controlled drug and is preservative-free, it may provide a convenient alternative to morphine by the extradural route. However, as a relatively larger dose of buprenorphine was needed, a frequency of side effects similar to that seen with morphine should be anticipated.

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EFFECT OF THE ADDITION OF ADRENALINE TO EXTRADURAL DIAMORPHINE ANALGESIA AFTER CAESAREAN SECTION

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SUMMARY

In a randomized double-blind study the effect of the addition of adrenaline to extradural diamorphine was assessed in 54 patients after Caesarean section. Patients received extradural diamorphine 5 mg in saline 10 ml with or without adrenaline 1 in 200 000 for postoperative pain relief. Analgesia was profound and of rapid onset in both groups. Duration of analgesia was greater in the adrenaline group (time to next analgesia 12.51 ± 0.94 h, mean ± SEM), than in the saline group (9.87 ± 0.98 h) (P = 0.057). Analgesia was also more consistent in the adrenaline group, with 77% of patients having more than 8 h of good analgesia compared with 48% in the saline group (P < 0.05). Plasma morphine concentrations, measured in 12 patients, were lower, although not significantly so, in the adrenaline group and mean time to peak concentration markedly delayed. No serious side effects were observed, but there was a higher incidence of vomiting in the adrenaline group.

Extradural opioid analgesia has a number of advantages over conventional i.m. administration, including a longer duration of action, greater intensity of analgesia and less sedation [1].

The extradural administration of a highly lipid soluble agent such as diamorphine, which is rapidly taken up into neural tissue, appears to minimize the risk of late respiratory depression—which is more commonly seen with hydrophilic agents such as morphine. The hydrophilic agents pass only slowly into neural tissue, thus tending to linger within the cerebrospinal fluid (CSF) with increased likelihood of rostral spread to the respiratory centre in the brain stem [2]. This advantage of diamorphine is partly offset, however, by the effect of rapid systemic absorption from the extradural space, which results in less drug being available for dural transfer and access to the opiate receptors within the spinal cord [3]. The effect of this decreased dural transfer is a shorter and less reliable duration of analgesia.

The addition of a vasoconstrictor such as adrenaline 1 in 200000 is commonly used to decrease systemic uptake of local anaesthetic agents from the extradural space and thus intensify the block. The addition of adrenaline to extradural diamorphine may produce a similar effect. This double-blind study was designed to establish the effect of the addition of adrenaline 1 in 200000 to extradural diamorphine 5 mg on duration of analgesia, frequency of adverse effects and plasma morphine concentrations.

PATIENTS AND METHODS

Fifty-four patients (ASA grades I or II) who had undergone Caesarean section under lumbar extradural blockade consented to take part in the study, which was approved by the hospital ethics committee. Lumbar extradural blockade was established, before operation, using 0.5% plain bupivacaine. Although no opioid or sedative drug was administered for at least 4 h before surgery,

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eight patients in the saline group (see below) and nine in the adrenaline group (see below) received small increments of midazolam (up to 5 mg) as a sedative following delivery.

Patients were instructed to request analgesia when they began to feel pain as the local anaesthetic block receded. At this point an anaesthetist observer (S.M. on each occasion) visited the patient and made an initial assessment. This consisted of an assessment of pain, using a 10-cm linear analogue pain score (LAPS) [4] and a four-point rank pain score (RPS) (none = 0; mild = 1; moderate = 2; severe = 3); and sedation using a four-point rank sedation score (RSS) (wide awake = 0; drowsy = 1; very drowsy = 2; sleeping = 3). In addition, heart rate, arterial pressure, ventilatory rate and the presence of any adverse effects were noted.

Patients were then randomly allocated to one of two analgesic regimens, to receive extradural diamorphine 5 mg in 0.9 % sodium chloride 10 ml either with or without adrenaline 1 in 200000. Sodium chloride was used instead of water in order to render the solution isotonic and, although the manufacturers of diamorphine (Evans) recommend water as a solvent, it has been shown that diamorphine can be reconstituted in 0.9 % sodium chloride safely [5]. The randomization was carried out by the hospital pharmacy who prepared unmarked ampoules containing diamorphine in either saline alone or saline with adrenaline; thus both anaesthetist and patient were unaware of the nature of the injectate. Assessments of pain and sedation were then repeated at 15, 30 and 60 min and at 2, 4, 8 and 12 h after injection. At the same times heart rate, arterial pressure and ventilatory rate were recorded and any adverse effects were noted.

Patients were told to request additional analgesia either if pain persisted or when it recurred. The time was noted and they were given an i.m. injection of morphine 10 mg, with cyclizine 50 mg (Cyclimorph 10) and withdrawn from the study.

In addition, 12 of the subjects (six in each group) had venous blood sampled for plasma morphine estimation before extradural injection and again at 3, 6, 10, 15, 20, 30, 45, 60, 120 and 240 min after injection. Since diamorphine is very rapidly metabolized to monoacetyl morphine and morphine, the increase in plasma morphine concentration accurately reflects the systemic absorption of diamorphine [6]. Plasma morphine concentrations were measured by high pressure liquid chromatography [7].

Results were subjected to statistical analysis by Student's *t* test or by Chi-squared test with Yates' correction as appropriate.

RESULTS

The two groups of patients (27 in each group) were similar in age (27 ± 0.92 yr and 27.7 ± 0.94 yr (mean ± SEM)) and weight (74.2 ± 2.7 kg and 70.6 ± 1.9 kg) in the saline and adrenaline groups, respectively. The onset of analgesia was rapid in

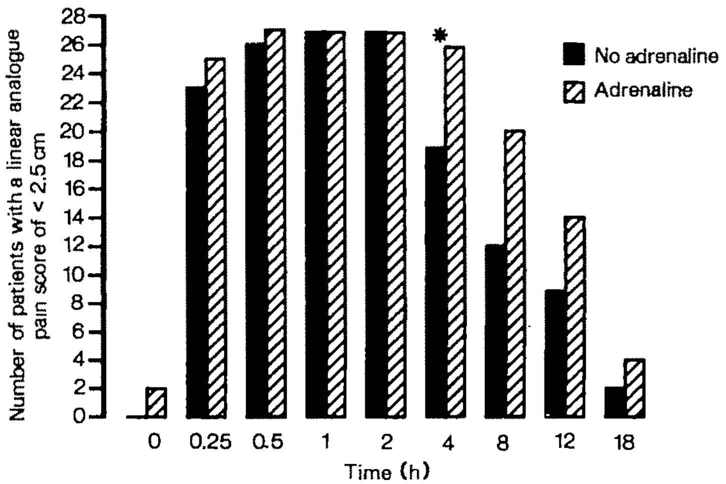

FIG. 1. Numbers of patients achieving a linear analogue pain score of < 2.5 cm up to 18 h after receiving extradural diamorphine with or without adrenaline. *Significant difference between groups (Chi-squared test with Yates' correction): $P < 0.05$.

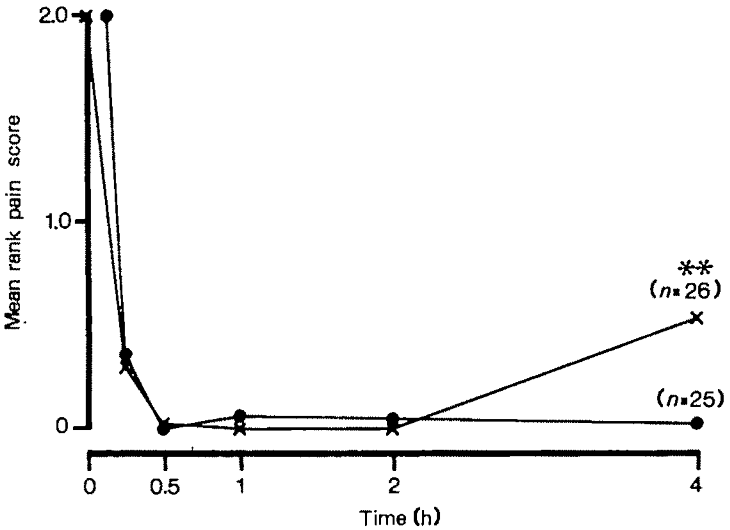

FIG. 2. Mean rank pain scores up to 4 h. x = Extradural diamorphine in saline; ● = extradural diamorphine with adrenaline. $^{**}P < 0.01$ (Chi-squared test with Yates' correction).

TABLE I. *Duration of analgesia.* $^{*}P = 0.057$ *(Student's t test);* $^{**}P < 0.05$ *(Chi-squared test with Yates' correction)*

Extradural group	Time to next analgesia (Mean ± SEM) (h)	Patients having more than 8 h analgesia (n, %)
Diamorphine + saline	9.87 ± 0.98*	13 (48)
Diamorphine + adrenaline	12.51 ± 0.94	21 (77)**

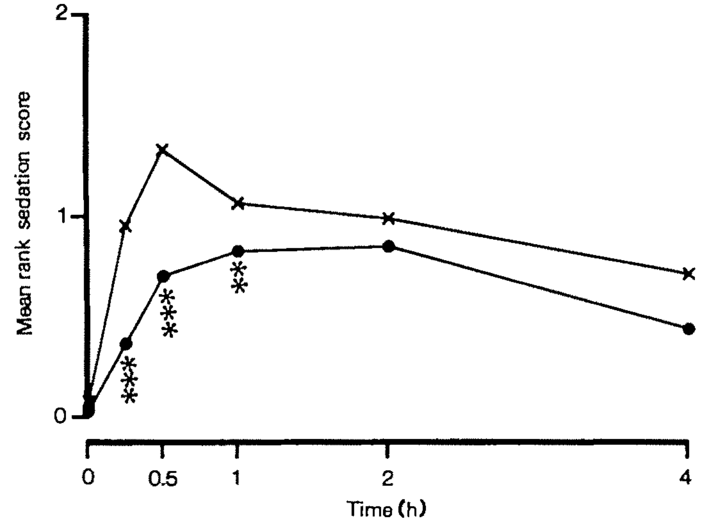

FIG. 3. Mean rank sedation scores up to 4 h. x = Extradural diamorphine in saline; ● = extradural diamorphine with adrenaline. $^{**}P < 0.01$; $^{***}P < 0.001$ (Chi-squared test with Yates' correction).

TABLE II. *Mean peak plasma morphine concentration* (Cp^{max}) *and time to peak* (T^{max}) *after extradural diamorphine with and without adrenaline* (±*SEM*). *P < *0.05* (t *test*)

Extradural group	Cp^{max} (ng ml^{-1})	T^{max} (min)
Diamorphine + saline	5.48 ± 1.27	35.8 ± 8.89
Diamorphine + adrenaline	4.42 ± 0.62	78.33 ± 19.39*

all patients, with significant decreases in both LAPS and RPS by 15 min (figs 1, 2). The number of patients achieving satisfactory analgesia (as manifested by an LAPS of less than 2.5 cm) demonstrated no difference between the two groups until 4 h, when significantly more patients had satisfactory analgesia in the adrenaline group (fig. 1). Maximum reduction in RPS in both groups occurred by 30 min, with the adrenaline group showing significantly lower pain scores at 4 h (fig. 2).

Duration of analgesia, as measured by time to next analgesia (table I), was greater in the adrenaline group, with a mean duration of action of 12.5 h compared with just under 10 h for the saline alone group. This difference however, just failed to achieve statistical significance ($P = 0.057$). Duration of analgesia was more consistent in the adrenaline group, with 77% having more than 8 h analgesia, compared with only 48% in the saline alone group ($P < 0.05$).

An increase in the degree of sedation occurred with onset of analgesia in both groups (fig. 3). The adrenaline group showed significantly lower sedation scores at all times until 1 h—possibly indicating a reduction in systemic uptake of diamorphine.

The mean peak plasma morphine concentration in the adrenaline group was lower than in the saline group and the mean time to peak concentration markedly prolonged (table II). Nevertheless the absorption of diamorphine, as estimated from the area under the plasma morphine concentration–time curve, was not significantly decreased by the addition of adrenaline (fig. 4).

Adverse effects are shown in table III. There were no significant changes in either arterial pressure or heart rate. A slight decrease in ventilatory rate occurred with the onset of analgesia in both groups, and the only significant difference between the groups was at 8 h with a higher rate in the saline group (20.46 ± 2.37 cf. 18.46 ± 1.84), possibly reflecting a waning of analgesic effect. Only one patient had a ventilatory rate of less than 12 b.p.m. and this occurred at 2 h in the saline group (11 b.p.m.). Itching achieved a combined incidence of 36%, there

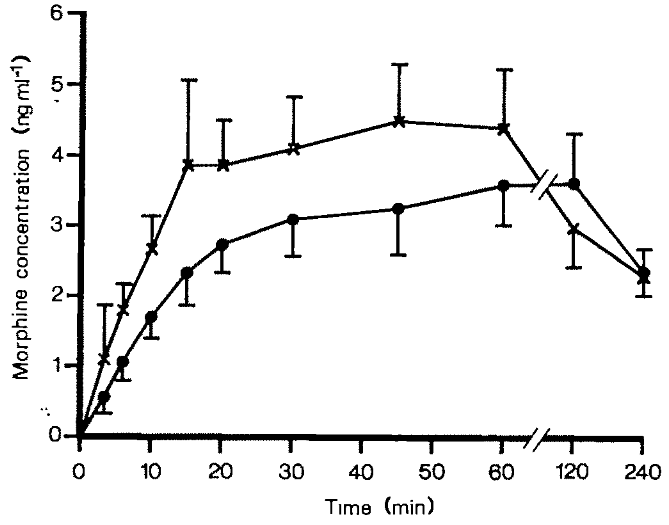

FIG. 4. Plasma morphine concentrations (ng ml^{-1}) up to 4 h (mean ± SEM). x = Extradural diamorphine in saline; ● = extradural diamorphine with adrenaline. No significant difference in area under curve.

TABLE III. *Adverse effects (No. of patients).* *P < 0.05 *(Chi-squared test, with Yates' correction)*

	Extradural diamorphine	
Adverse effect	+saline	+adrenaline
Nausea	4	4
Vomiting	1	8*
Itching	11	9
Ventilatory rate < 12 b.p.m.	1	0
Heart rate < 60 beat min^{-1}	0	0
Systolic arterial pressure decrease > 20 %	0	0

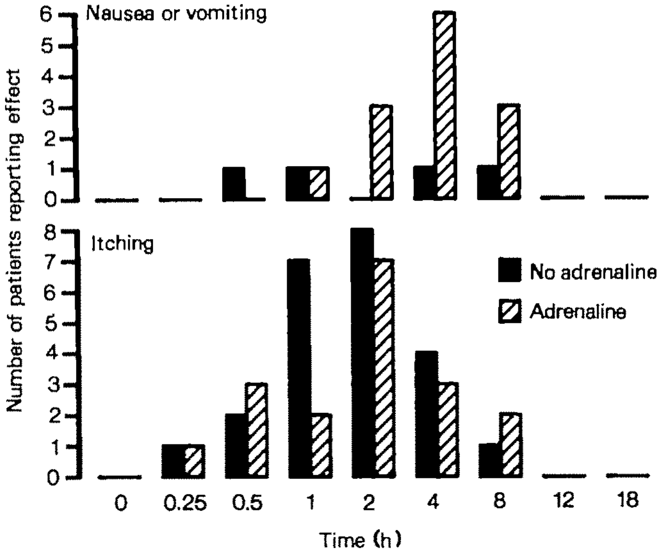

FIG. 5. Incidence of nausea and vomiting and itching up to 18 h, in patients who received extradural diamorphine with or without adrenaline.

being no difference between groups (fig. 5). This symptom was, however, sought by direct questioning and was at no time troublesome enough to require treatment.

The only marked difference was seen in the incidence of nausea and vomiting (fig. 5). Although nausea alone was present in four subjects in each group, far more vomited in the adrenaline group, namely eight, compared with only one in the saline group. Only one patient required an anti-emetic. No other serious adverse effect was reported.

DISCUSSION

We have demonstrated that the addition of adrenaline to extradural diamorphine delays systemic absorption of the diamorphine, with consequent reduction in early systemic effects such as sedation and, possibly by increasing dural transfer, produces more predictable analgesia of longer duration. The higher incidence of vomiting occurring with the addition of adrenaline may also reflect the increased dural transfer, and higher CSF concentrations.

Extradural diamorphine has been shown to provide analgesia of greater intensity and longer duration than i.m. diamorphine in patients following Caesarean section [1]. In that study, although the mean duration of analgesia provided by extradural diamorphine (8.39 h) was significantly longer than that provided by i.m. diamorphine (3.40 h), analgesia was of short duration in several patients in the extradural group, possibly as a result of the rapid systemic uptake of diamorphine from the extradural space. This uptake is especially likely to occur in obstetric patients in whom extradural blood flow is known to be high [8].

The *in vitro* evidence of Moore and co-workers [9] suggested that dural transfer was primarily a process of simple diffusion and was, therefore, dependent on the presence of a concentration gradient to drive drugs across the dura. If systemic absorption is rapid, then the concentration gradient across the dura will be rapidly reduced and relative dural transfer will be low [3, 10]. The validity of the model introduced by Moore and colleagues has been challenged [11], and alternative routes of transfer of opioids from the extradural space to the neural tissue of the spinal cord—via the arachnoid granulations or the posterior radicular arteries—cannot be excluded on currently available evidence.

A potential way of achieving more reliable dural transfer would be to retain diamorphine in the extradural space for a longer time and this study was designed to establish whether the addition of adrenaline to the diamorphine could achieve this. Previous reports of the addition of adrenaline to extradural opioids have produced conflicting results. Perriss and Malins [12] reported that 83% of patients given extradural pethidine with adrenaline while in labour had satisfactory analgesia. Skjoldebrand and colleagues [13] found no difference between extradural pethidine with and without adrenaline and further concluded that extradural pethidine was inferior to extradural local anaesthetic for analgesia in labour. Martin and co-workers [14] reported that extradural morphine 2 mg with adrenaline did not provide satisfactory analgesia in labour. Bromage and colleagues [15], however, reported that the addition of adrenaline to extradural morphine 10 mg reduced vascular absorption and intensified all manifestations of its administration including adverse effects, in three volunteers. Welchew [16] demonstrated that the addition of adrenaline to extradural injections of fentanyl increased their effect at low concentrations. The author attributed this left shift in the dose–response curve for fentanyl to a reduction in systemic absorption produced by adrenaline.

One reason for the differing effects seen with the addition of adrenaline to extradural opioids may be the relative lipid insolubility of morphine and pethidine. Their systemic absorption is much slower than the more lipid soluble diamorpine and fentanyl, and the addition of adrenaline to these latter agents may have a more pronounced effect.

In this study we have shown that adrenaline delays the systemic absorption of diamorphine from the extradural space, with a significantly longer time to peak plasma morphine concentration than with diamorphine alone. This difference in systemic absorption parallels the difference in opioid effects which we found between the two groups. It is of interest that the plasma morphine concentrations were much lower than the mean effective analgesic concentration of morphine (16 ng ml^{-1}) [17] and, also, much lower than those of Watson and colleagues [3] who used a similar dose of extradural diamorphine. The reason for the difference between our results and those of Watson and colleagues [3] probably lies in the nature of the assays used. The radioimmunoassay used by Watson and colleagues may have detected, not only morphine, but also monoacetyl morphine, morphine-3-glucuronide and morphine-6-glucuronide, whereas our assay was specific for morphine. Since diamorphine is rapidly metabolized to monoacetyl morphine and morphine, it is assumed that plasma morphine concentrations are a valid measure of the systemic absorption of diamorphine [6]. The significantly lower rank sedation scores in the adrenaline group at 0.25, 0.5 and 1.0 h probably reflect this delay in systemic absorption and the resulting central effects.

The improved predictability of analgesia seen in the adrenaline group, with 77% of patients having satisfactory analgesia at 8 h compared with 48% in the saline group, was also reported by Perriss using extradural pethidine with adrenaline in labour, where the addition of adrenaline increased the number of patients having good pain relief from 43% to 83% [12, 18].

No major adverse effects were encountered in this study. Of the minor effects encountered, the incidence of itching was similar in the two study groups and the combined incidence of 37% is comparable to reported series in which patients were directly questioned [1, 19]. We were surprised to note the high incidence of vomiting in the adrenaline group. However, despite the evidence available indicating rapid clearance of diamorphine from the cerebrospinal fluid [2], presumably into the spinal cord, it must be assumed that either diamorphine or one of its active metabolites, such as morphine, persists in the cerebrospinal fluid and, by cephalad flow, reaches the brain stem to encroach on the vomiting centre. Vomiting was most commonly reported at times between 2 and 8 h (fig. 5). The time interval between lumbar injection of radionucleotides and spread to the brain stem is 3–6 h [20, 21]. It is likely, therefore, that the higher incidence of vomiting in the adrenaline group reflects higher relative dural transfer of diamorphine, enhanced drug concentrations in spinal compartments including CSF, and increased rostral spread in the CSF. Notwithstanding the higher incidence of vomiting, it is the opinion of the obstetric anaesthetists here that the benefits of more consistent, prolonged analgesia outweigh the disadvantages of this side effect in some patients, and extradural diamorphine in adrenaline is now routinely used in this situation.

We found no evidence of late respiratory depression in either group. Previous studies using extradural diamorphine via lumbar [1] or mid-thoracic [22] routes have similarly been free of this complication. However, published series of the administration of extradural diamorphine are few in number. Nevertheless, a case of excessive sedation and respiratory depression following the thoracic extradural injection of diamorphine has been reported [23], and respiratory monitoring is advised [23].

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INTRATHECAL MORPHINE IN THE MANAGEMENT OF PAIN FOLLOWING CARDIAC SURGERY

A Comparison with Morphine I.v.

G. J. FITZPATRICK AND D. C. MORIARTY

There is ample evidence to show that the intrathecal administration of morphine produces good analgesia in a variety of clinical situations [1–3]. By this route, morphine binds to opioid receptors within the spinal cord [4] and the degree of analgesia would seem to be related to the high concentration of the drug in the cerebrospinal fluid [5, 6].

While the clinical use of intrathecal morphine was still being developed, reports appeared of concomitant respiratory depression [7, 8] and it rapidly became obvious that this risk would limit the use of the technique to specific clinical situations.

Cardiac surgery is a specialty in which the use of intrathecal opioids would seem advantageous. The pain after median sternotomy may be severe and difficult to control [9] and, as these patients are monitored carefully in the Intensive Care Unit, one would expect to detect and treat respiratory depression before there was any significant risk to the patient. Mathews and Abrams [10] reported favourable results with intrathecal morphine given to patients after cardiac surgery in doses ranging from 1.5 mg to 4 mg, while Aun and colleagues [11] compared 2 mg with 4 mg and concluded that 4 mg was a more appropriate dose.

However, as the risk of side effects with intrathecal morphine appears to be dose-related [12, 13] it was decided to study the effects of lower doses. This study investigated the analgesic and respiratory effects of intrathecal morphine in doses of 1 mg and 2 mg and compared this technique with a conventional analgesic regimen.

SUMMARY

Forty-four patients undergoing coronary revascularization received either intrathecal morphine 1 mg ($n = 15$), intrathecal morphine 2 mg ($n = 15$), or i.v. morphine 30 mg ($n = 14$) after the induction of anaesthesia. Morphine 2.5 mg i.v. was given, as required, in the postoperative period and pain score, respiratory rate and Pa_{CO_2} measured every 2 h. FVC, FEV_1 and PEFR were measured before, and 24 h after, the induction of anaesthesia. Mean overall pain scores in both intrathecal groups were significantly lower than in the i.v. group ($P < 0.01$), but did not differ significantly between the intrathecal groups. Consumption of supplementary morphine was significantly lower in both intrathecal groups ($P < 0.01$). Mean Pa_{CO_2} was significantly higher in patients given intrathecal morphine 2 mg. This was significant at 12, 14 and 16 h after induction of anaesthesia. Respiratory rate did not differ significantly between the groups. Postoperative PEFR was significantly better in patients given intrathecal morphine ($P < 0.01$). These results suggest that intrathecal morphine provided better analgesia after cardiac surgery than did a conventional regimen. The lower dose (1 mg) was associated with less respiratory depression as assessed by Pa_{CO_2} measurements.

PATIENTS AND METHODS

Forty-five male patients undergoing cardiac surgery were studied. All gave informed consent and the study was approved by the hospital ethics committee. Patients with co-existing respiratory disease or ventricular dysfunction (ejection fraction < 0.4) were excluded. Preoperative measurements were made of arterial oxygen (Pa_{O_2}) and

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carbon dioxide (Pa_{CO_2}) tensions, ventilatory rate, peak expiratory flow rate (PEFR), forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1). Patients were instructed in the use of the visual linear analogue scale for pain [14].

After premedication with lorazepam 4 mg by mouth, general anaesthesia was induced with midazolam 5–10 mg and thiopentone 2–4 mg kg^{-1}, and maintained with 60% nitrous oxide in oxygen, supplemented with a low concentration of halothane, enflurane or isoflurane. Pancuronium 0.2 mg kg^{-1} was given and the trachea intubated with a 9.0-mm cuffed tracheal tube. Ventilation (to normocapnia) was provided using a Barnett Mk 4 ventilator. Arterial pressure was controlled throughout with an infusion of nitroglycerine i.v. Fentanyl 250 µg was administered, if required.

Using tables of random numbers, the patients were allocated to one of three treatment groups: A, B or C. After intubation, patients in groups A and B were turned to the left lateral position and received an intrathecal injection of preservative-free morphine 1 mg 5 ml^{-1} through a 25-gauge needle inserted at the L3–4 space. Patients in group A ($n = 15$) received morphine 1 mg and those in group B ($n = 15$) received 2 mg. Patients in group C ($n = 15$) remained in the supine position and were given morphine sulphate 30 mg i.v. over a period of 15 min (IVM). All patients were transferred to the operating theatre where the surgical procedure was carried out under cardiopulmonary bypass with moderate hypothermia (28 °C).

On completion of surgery patients were transferred to the intensive care unit, where artificial ventilation was continued with 50% oxygen in nitrous oxide. All patients received cyclizine 50 mg i.v. on arrival in the intensive care unit and staff nurses were instructed to give morphine i.v. in increments of 2.5 mg, as required.

When body temperature had returned to normal, and the patients were haemodynamically and biochemically stable, nitrous oxide was discontinued and the patients allowed to waken and breathe spontaneously. The inspired oxygen concentration (FI_{O_2}) was adjusted to maintain Pa_{O_2} between 10 and 14 kPa. The tracheal tube was removed when breathing was adequate and the patients sufficiently alert. Oxygen was administered by facemask to maintain Pa_{O_2} within normal limits. Decisions regarding weaning and extubation were made by the anaesthetist on duty in the intensive care unit, who was not aware of which treatment had been administered.

After extubation, Pa_{O_2}, Pa_{CO_2}, ventilatory rate and the visual linear analogue pain score were measured. These measurements were repeated at intervals of 2 h and continued for up to 24 h after the induction of anaesthesia. Patients were questioned at the same intervals about the presence of side effects, in particular nausea, vomiting, pruritus, headache and drowsiness. The amount of morphine administered i.v. to each patient during the study period was recorded.

Postoperative measurements of FVC, FEV_1 and PEFR were made 24 h after the induction of anaesthesia in those patients who were relatively pain free at rest (pain score $\leqslant 3$). In patients who complained of pain at rest (pain score > 3) the pulmonary function tests were performed 30 min after the administration of morphine 2.5 mg i.v.

RESULTS

Of the 45 patients who entered the study, one patient in group C required further surgery during the study period and was excluded from the results. There were no differences between the groups with respect to age, weight, type of operation performed or duration of surgery (table I).

Analgesia

Figure 1 shows the mean pain score for each group of patients at each assessment time. Between 14 and 24 h after induction of anaesthesia,

TABLE I. *Patient details. ITM = Intrathecal morphine; IVM = i.v. morphine*

	Group A 1 mg ITM	Group B 2 mg ITM	Group C IVM
Number	15	15	14
Age (yr)			
Mean ± SD	50 ± 11.2	52 ± 9.7	52 ± 7.1
Range	25–67	31–63	42–64
Wt (kg)			
Mean ± SD	78 ± 9.7	82 ± 10.3	82 ± 8.6
Range	58–92	60–101	70–100
Aortic valve replacement	3	2	0
Coronary revascularization	12	13	14
Duration of surgical procedure (h)			
Mean ± SD	3.9 ± 0.57	4.1 ± 0.64	4.1 ± 0.82
Range	3–5.25	3–5	3–6

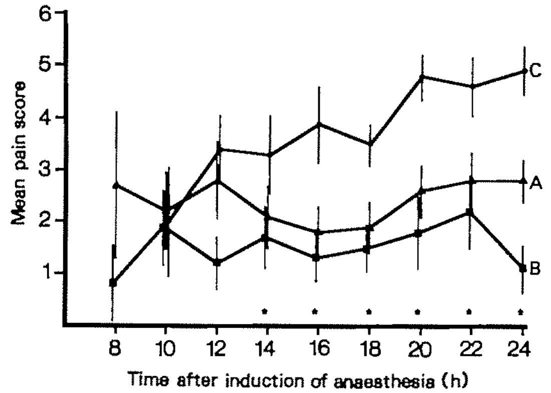

FIG. 1. Mean (±SEM) pain score (10-cm linear analogue scale) in groups A (intrathecal morphine 1 mg), B (intrathecal morphine 2 mg) and C (i.v. morphine) at each assessment time during the study period. *Significant difference between A and C: $P < 0.05$.

pain scores in both intrathecal groups were significantly lower than in the i.v. group. Furthermore, the overall mean pain score (table II) was significantly lower in both of the groups given intrathecal morphine ($P < 0.01$).

The consumption of supplementary morphine by each patient during the study period is recorded in figure 2. The requirement for additional analgesia was significantly higher in group C than in either of the intrathecal groups ($P < 0.01$). Six patients in group A and eight patients in group B (the intrathecal groups) required no supplementary analgesia during the study period.

There was a tendency for the trachea to be extubated earlier in the patients given intrathecal morphine (table III) and, in this respect, the difference between group A and group C was statistically significant ($P < 0.05$).

Pulmonary function was considerably decreased in the postoperative period in all patients (table IV). However, the peak expiratory flow rate 24 h after induction of anaesthesia was significantly better in both of the groups of patients given intrathecal morphine ($P < 0.01$). The difference between the groups with respect to FVC and FEV_1 were not statistically significant.

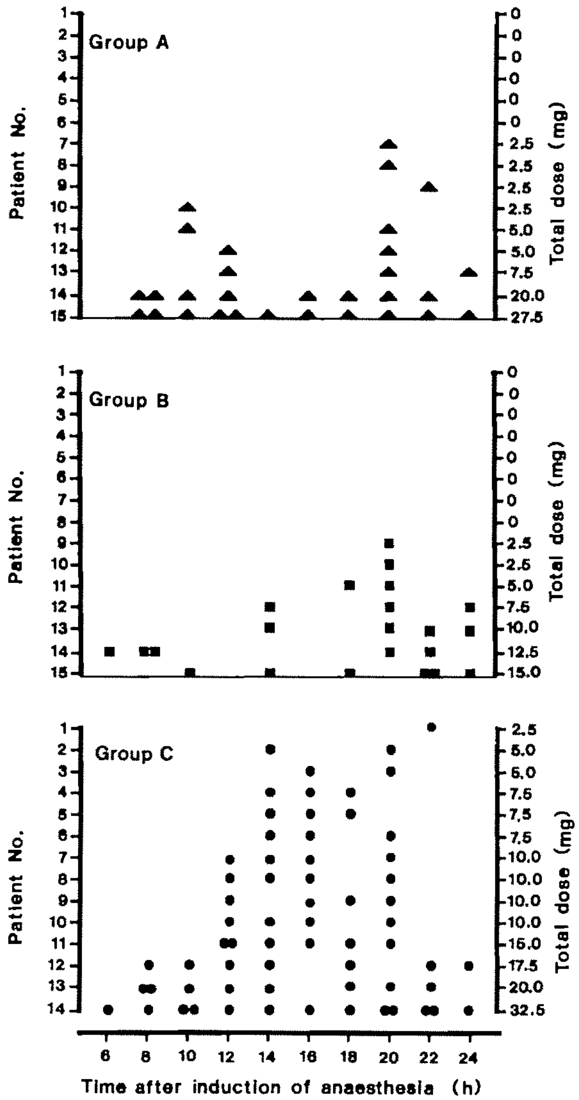

FIG. 2. Supplementary morphine consumption by individual patients as a function of time. Each symbol represents an i.v. injection of morphine 2.5 mg. The total dose given to each patient is given in the right hand column. Group A = intrathecal morphine 1 mg; group B = intrathecal morphine 2 mg; group C = i.v. morphine.

TABLE II. *Mean (±SEM) overall pain score (10-cm linear analogue scale) in each group of patients. ITM = Intrathecal morphine; IVM = i.v. morphine: *Significantly lower than group C: P <0.01*

	Group A 1 mg ITM	Group B 2 mg ITM	Group C IVM
Pain score	2.46±0.46*	1.56±0.36*	4.0±0.4

Respiratory effects

The mean Pa_{CO_2} for each group of patients at each assessment time is shown in figure 3. In groups A and C, mean Pa_{CO_2} remained within

TABLE III. *Interval (h) from end of surgery to extubation. ITM = Intrathecal morphine; IVM = i.v. morphine (mean ± SEM). *Significantly different from group C*: $P < 0.05$

	Group A 1 mg ITM	Group B 2 mg ITM	Group C IVM
Time to extubation	5.7 ± 0.43*	6.5 ± 0.65	8.2 ± 0.72

TABLE IV. *Mean postoperative respiratory function expressed as a percentage of preoperative values (± SEM). *Significantly higher than in group C*: $P < 0.01$

	Group A 1 mg ITM	Group B 2 mg ITM	Group C IVM
PEFR	48 % ± 2.7*	52 % ± 3.5*	35 % ± 2.5
FVC	32 % ± 2.9	37 % ± 4.3	22 % ± 2.9
FEV_1	32 % ± 3.1	37 % ± 4.4	30 % ± 2.7

relatively normal limits throughout the study period, but in group B (intrathecal morphine 2 mg) mean Pa_{CO_2} remained above 6.0 kPa until 16 h after the induction of anaesthesia. The differences in mean Pa_{CO_2} between group A and group C were not statistically significant. However, in group B the mean overall Pa_{CO_2} and the mean Pa_{CO_2} values measured at 12, 14 and 16 h were significantly higher than in either of the other groups ($P < 0.01$).

There was no difference between the groups with respect to ventilatory rates (fig. 4).

Two patients, one in each intrathecal group, developed respiratory depression requiring treatment with naloxone. These will be discussed below.

The incidence of minor side effects occurring during the study period is shown in table V. Nausea and vomiting occurred in 23 % of patients given intrathecal morphine. Pruritus tended to occur more frequently in patients given intrathecal morphine 2 mg, but was mild in all cases. Two patients in group B complained of mild headache during the study period. Several patients in each group complained of minor transient headaches over the following 2 days, but one patient in group B complained of a typical spinal headache which persisted throughout most of the first postoperative day.

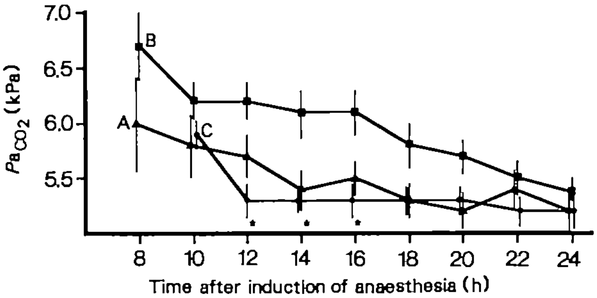

FIG. 3. Mean (± SEM) Pa_{CO_2} (kPa) at each assessment time during the study period. Group A = intrathecal morphine 1 mg; group B = intrathecal morphine 2 mg; group C = i.v. morphine. *Significant difference between groups A and B: $P < 0.05$.

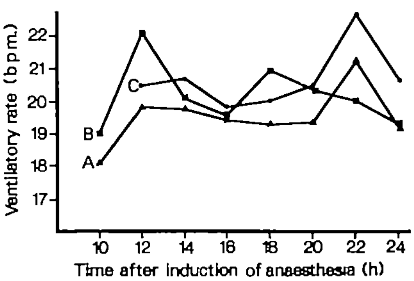

FIG. 4. Mean ventilatory rate at each assessment time in groups A (intrathecal morphine 1 mg), B (intrathecal morphine 2 mg) and C (i.v. morphine).

TABLE V. *Number of patients displaying side effects during the study period. ITM = Intrathecal morphine; IVM = i.v. morphine*

	Group A 1 mg ITM ($n = 15$)	Group B 2 mg ITM ($n = 15$)	Group C IVM ($n = 14$)
Nausea	3	2	None
Vomiting	1	1	None
Drowsiness	8	11	7
Pruritus	1	4	None
Headache	None	2	None

DISCUSSION

Anaesthesia for cardiac surgery presents many challenges to the anaesthetist, not the least of which is the control of postoperative pain. Pain relief is necessary not only for the patient's comfort, but also to ensure adequate respiration and to facilitate the clearing of bronchial secretions.

Intrathecal morphine, with its ability to provide intense long-lasting analgesia, would be useful in cardiac surgery, provided the patient was not put at increased risk. Early work with intrathecal morphine involved doses up to 20 mg [15], while more recent studies have tended towards a smaller dose [3, 16]. There is good reason for this recent trend, in that the incidence of side effects, in particular respiratory depression, appears to be related to dose [12, 13]. We would consider the optimum dose of intrathecal morphine to be the dose which provides effective analgesia with a minimum risk of respiratory depression. It is likely that this will vary in different clinical situations.

This study demonstrated that intrathecal morphine in a dose of either 1 mg or 2 mg provided effective analgesia after cardiac surgery. When the low pain scores are considered in conjunction with the reduced requirement for supplementary morphine and the significantly better postoperative peak flow rate, it is evident that the use of intrathecal morphine afforded better control of pain than did the i.v. regimen. Figure 2 shows that six patients in group A and eight patients in group B required no additional analgesia during the first 24 h. However, two patients in group A (figure 2, patients Nos 14 and 15) did not have satisfactory control of pain. This is not readily explicable. One of these patients weighed 79 kg and it could be argued that 1 mg of intrathecal morphine was not sufficient to provide adequate analgesia. However, the other patient weighed only 58 kg and possible causes of inadequate analgesia must include inadequate delivery of the drug to the CSF, a low individual pain threshold, or both. The increase in requirement for supplementary morphine in the intrathecal groups during the last 4 h of the study period would correspond with the decline in CSF concentration [6].

The tendency for earlier extubation of the trachea in patients given intrathecal morphine 1 mg (earlier, that is, than those in the i.v. group) may be the result of a variety of factors. We believe that effective analgesia combined with a lower level of neurological depression were important in achieving earlier extubation.

Samii and colleagues [15] and Gjessing and Tomlin [17] have observed respiratory depression after intrathecal morphine to be dose-related. In the present study, one patient in each intrathecal group required treatment with naloxone for respiratory depression. Both these patients were moderately drowsy, with an increased Pa_{CO_2}—but were in a stable cardiovascular condition. Naloxone 0.4 mg was administered to each patient with good effect and it was interesting that the administration of naloxone did not alter the quality of analgesia in either. This phenomenon has been reported by others [18].

We have demonstrated that the Pa_{CO_2} was greater in patients given intrathecal morphine than in controls (fig. 3). In group B (intrathecal morphine 2 mg), mean Pa_{CO_2} was greater than normal for up to 16 h after induction and was significantly greater than in group A or group C. This finding suggests that the risk of respiratory depression will be greater when the larger dose is used. Considering the changes in Pa_{CO_2}, one might have expected to observe a decrease in respiratory rate in those given intrathecal morphine 2 mg. In fact, there was no significant difference between the groups with respect to ventilatory rate. There are two possible explanations for this. First, the patients had been aroused by the observer to enquire about side effects when the ventilatory rates were measured and this arousal may have led to an increase in the rate. Second, in studies using extradural narcotics it appears that a reduction in tidal volume rather than in rate of ventilation may be the main mechanism of depression of resting ventilation [19]. If this is true for extradural narcotics, it is likely also to be true for intrathecal morphine.

Pruritus is a well known side effect of spinal opioids, although the reported incidence varies considerably [11, 20]. In this study, pruritus tended to occur more frequently in patients given the larger dose (2 mg), but was mild in all cases.

Rostral spread of morphine within the cerebrospinal fluid may, in addition to producing respiratory depression, cause undue drowsiness [21]. Drowsiness occurred in a considerable proportion of patients in all three groups (table V), and the differences between the groups were not significant.

Nausea and vomiting may occur after the administration of spinal morphine. This may be the result of the morphine spreading centrally within the cerebrospinal fluid and affecting the vomiting centre and the chemoreceptor trigger zone [12, 22]. A previous unpublished survey in this unit found that nausea and vomiting occurred in 40 % of patients who had been given intrathecal morphine and was quite severe in many. In the present series, all patients received an antiemetic (cyclizine) on completion of surgery. The incidence of nausea and vomiting was 23 %, but was mild in all cases.

Recently, attention has been drawn to the danger of subarachanoid haematoma after lumbar puncture and heparinization [23]. In this unit to date, more than 3400 patients have received intrathecal morphine followed by systemic heparinization, and no patient has developed signs of subarachanoid or extradural haematoma. All lumbar punctures were performed with a 25-gauge needle and the shortest interval between lumbar puncture and heparinization was 50 min.

To conclude, we have found the use of intrathecal morphine to be a safe and effective method of providing analgesia after cardiac surgery. When compared with the conventional regimen, intrathecal morphine is associated with better control of pain, the evidence for this being the lower pain scores, the decreased requirement for supplementary analgesia and the better postoperative peak flow rate. Although the pain scores were slightly better with the larger dose (2 mg) they were not significantly so, and this dose was associated with a significantly higher Pa_{CO_2}. Finally, before the place of intrathecal morphine is fully defined, information is required on its effects on metabolic stress and haemodynamic variables.

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INFLUENCE OF DEXTRAN ON THE ABSORPTION OF ADRENALINE-CONTAINING LIGNOCAINE SOLUTIONS: A PROTECTIVE MECHANISM IN LOCAL ANAESTHESIA

H.-A. ADAMS, J. BISCOPING, H. KAFURKE, H. MÜLLER, B. HOFFMANN, U. BOERNER AND G. HEMPELMANN

SUMMARY

The effect of adding 6% dextran to a lignocaine solution containing adrenaline was studied in 27 neurosurgical patients during modified neurolept-anaesthesia. Before trepanation they received infiltration anaesthesia of the scalp at the site of the proposed operation. For a period of 1 h following injection plasma concentrations of adrenaline were measured by high pressure liquid chromatography and serum concentrations of lignocaine by gas chromatography. The addition of dextran caused a significant reduction in the absorption of both adrenaline and lignocaine from the injection site. It is concluded that the dextran adjuvant constitutes a protective mechanism against toxic systemic side effects in local anaesthesia using adrenaline-containing anaesthetic solutions. This effect is particularly significant in patients with pre-existing cardiovascular disease and when local anaesthetic solutions are used in combination with volatile anaesthetics.

The question of whether the addition of dextran prolongs the action or reduces the absorption of local anaesthetic solutions has been discussed since the appearance of Loder's study on this subject in 1960 [1]. He reported that the duration of action of locally injected lignocaine solutions used to relieve postoperative pain was increased by the addition of adrenaline 1:250000, and prolonged still further by the addition of 10% dextran. He claimed that the dextran adjuvant was more effective than the addition of adrenaline alone. When these substances were used in combination, a further additive effect was achieved. Loder carried out his tests on 41 patients after abdominal and thoracic surgery and seven patients following haemorrhoid operations using the pinprick method to determine the duration of analgesia. In a later paper [2] he reported on more than 300 post-thoracotomy patients, observing the postoperative demand for analgesics as criterion of efficiency.

German publications include a report by Nolte and colleagues [3] who found that the addition of dextran to various mepivacaine solutions improved the results in 12 patients with ulnar blockade. In this paper, he referred to clinical reports [4–7].

The present study was designed to clarify if the addition of dextran to a local anaesthetic solution containing adrenaline delays the absorption of adrenaline, delays the absorption of the local anaesthetic, or causes any measurable variation in circulatory responses.

PATIENTS AND METHODS

The study included 27 neurosurgical patients (ASA groups I–III) prepared for trepanation. Patients with severe impairment of the cardiovascular system were not admitted to the study.

After induction of a standardized, modified neuroleptanaesthetic technique, the surgeon infiltrated the scalp area intended for trepanation with 40 ml of the solution to be tested. Care was taken to avoid intravascular injection.

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The patients were allocated randomly to the following groups:

Saline group ($n = 10$): 2% lignocaine with adrenaline 1:50000, diluted 1:1 with 0.9% saline solution.

Dextran group ($n = 10$): 2% lignocaine with adrenaline 1:50000, diluted 1:1 with 6% dextran 60 in 0.9% saline solution (Plasmafusin 60).

Control group ($n = 7$): 0.9% saline solution.

The pH-values of the two local anaesthetic solutions were 3.65.

All samples were taken from a central venous catheter at the following intervals:

S1 = Immediately before injection
S2 = 5 min after injection
S3 = 10 min after injection
S4 = 20 min after injection
S5 = 30 min after injection
S6 = 45 min after injection
S7 = 60 min after injection

Plasma adrenaline and noradrenaline, and serum lignocaine concentrations were measured.

Heart rate and arterial pressure were monitored continuously after cannulation of a radial artery.

The determination of plasma catecholamines by high pressure liquid chromatography with electrochemical detection (HPLC-ECD) and of lignocaine by gas chromatography have been reported elsewhere [8–10].

The catecholamine and lignocaine values were log-transformed and evaluation was undertaken using the geometric mean values. Values of arterial pressure and heart rate are expressed as arithmetic mean. Statistical differences were determined using analysis of variance with repeated measures on one factor. *P* values less than 0.05 were considered significant.

RESULTS

Plasma adrenaline (table I)

The concentrations of plasma adrenaline in the dextran group were significantly lower than those in the saline group ($P < 0.0001$).

Differences in time courses of concentrations between both groups were also apparent ($P < 0.0001$).

Figure 1 illustrates the time course of adrenaline concentrations in all three groups, demonstrating main differences 5–20 min after the end of injection. A close approximation of the curves was achieved 60 min after the end of injection.

TABLE I. *Plasma adrenaline and noradrenaline, and serum lignocaine concentrations. Geometric mean values and ranges*

Time	Group	Adrenaline (pg ml^{-1})	Lignocaine (μg ml^{-1})	Noradrenaline (pg ml^{-1})
S1	Saline	23	—	116
		9–272	—	17–608
	Dextran	15	—	75
		3–49	—	9–502
	Control	13	—	236
		3–45	—	97–571
S2	Saline	2391	2.48	93
		853–8632	1.02–6.26	17–388
	Dextran	336	0.24	104
		56–1532	0.02–1.93	37–562
	Control	13	—	250
		3–153	—	130–529
S3	Saline	1779	1.96	106
		516–6771	0.75–6.15	24–421
	Dextran	206	0.18	119
		116–380	0.05–0.73	56–490
	Control	14	—	254
		3–90	—	152–497
S4	Saline	818	1.25	123
		260–4316	0.43–5.66	23–403
	Dextran	227	0.26	130
		92–695	0.11–1.19	48–810
	Control	19	—	245
		3–141	—	122–599
S5	Saline	630	1.14	113
		227–3076	0.37–4.84	33–361
	Dextran	197	0.23	120
		58–846	0.07–0.99	22–1252
	Control	22	—	264
		5–569	—	119–939
S6	Saline	430	0.82	129
		133–1486	0.29–2.50	40–352
	Dextran	167	0.23	134
		54–509	0.09–0.89	26–2116
	Control	14	—	277
		3–285	—	123–944
S7	Saline	242	0.69	127
		30–902	0.20–2.13	37–385
	Dextran	169	0.24	126
		36–664	0.07–0.80	30–318
	Control	19	—	305
		3–341	—	127–923

Serum lignocaine (table I)

The concentrations of lignocaine in the dextran group were significantly lower than those in the saline group ($P < 0.0001$). Differences in time course between the groups were also observed ($P < 0.0001$).

Figure 1 demonstrates a similar time course of adrenaline and lignocaine concentrations within the treatment groups.

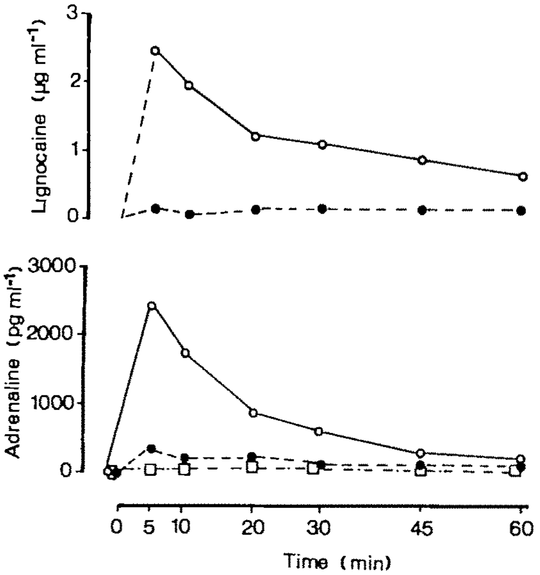

FIG. 1. Changes in plasma adrenaline and serum lignocaine concentrations after scalp infiltration with different solutions (geometric mean values). ● = Lignocaine + adrenaline + dextran ($n = 10$); ○ = lignocaine + adrenaline + saline ($n = 10$); □ = control ($n = 7$).

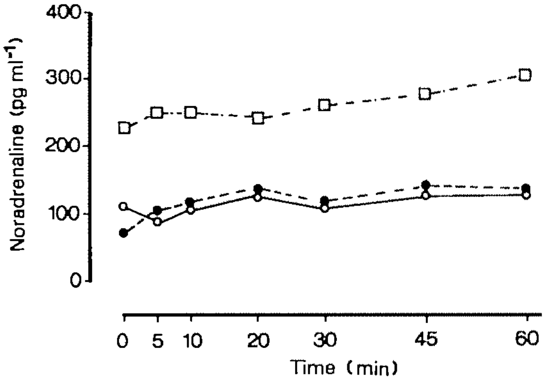

FIG. 2. Changes in plasma noradrenaline concentrations after scalp infiltration with different solutions (geometric mean values). ● = Lignocaine + adrenaline + dextran ($n = 10$); ○ = lignocaine + adrenaline + saline ($n = 10$); □ = control ($n = 7$).

TABLE II. *Heart rate (HR) and mean arterial pressure (MAP). Arithmetic mean values (standard deviations)*

Time	Group	MAP (mm Hg)	HR (beat min^{-1})
S1	Saline	95 (18)	71 (11)
	Dextran	102 (8)	65 (12)
	Control	100 (12)	73 (12)
S2	Saline	95 (15)	82 (19)
	Dextran	99 (7)	68 (13)
	Control	100 (12)	74 (12)
S3	Saline	90 (15)	81 (17)
	Dextran	95 (9)	67 (12)
	Control	103 (16)	77 (9)
S4	Saline	85 (14)	78 (15)
	Dextran	94 (15)	66 (11)
	Control	92 (10)	79 (13)
S5	Saline	88 (15)	73 (10)
	Dextran	94 (13)	66 (10)
	Control	91 (9)	78 (11)
S6	Saline	90 (15)	70 (5)
	Dextran	94 (15)	64 (9)
	Control	90 (7)	75 (8)
S7	Saline	92 (13)	68 (6)
	Dextran	95 (12)	65 (10)
	Control	90 (10)	75 (6)

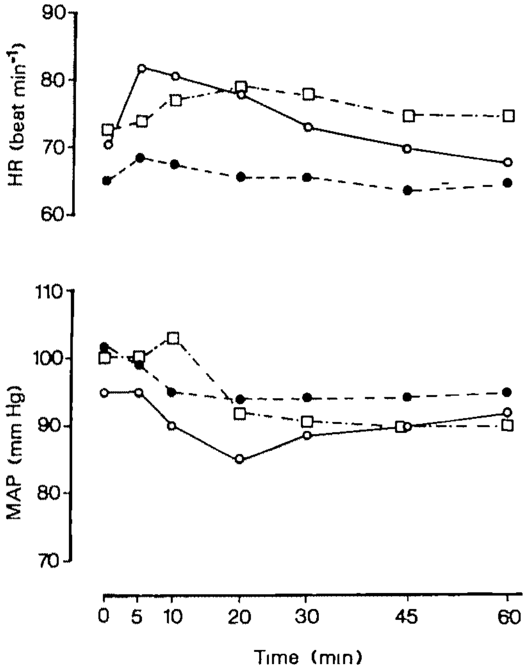

FIG. 3. Changes in heart rate (HR) and mean arterial pressure (MAP) after scalp infiltration with different solutions (arithmetic mean values). ● = Lignocaine + adrenaline + dextran ($n = 10$); ○ = lignocaine + adrenaline + saline ($n = 10$); □ = control ($n = 7$).

Plasma noradrenaline (table I)

There were no differences between the test groups in noradrenaline concentrations and time course. No significant change in noradrenaline concentrations within the test groups was observed (fig. 2).

Mean arterial pressure (table II)

There were no significant differences in mean arterial pressure with respect to mean values and course of time (fig. 3).

Heart rate (table II)

Differences in mean values of heart rate were not significantly different ($P = 0.08$), but the changes in time course did reach statistical significance ($P = 0.04$).

Figure 3 shows the higher values of heart rate in the saline group compared with the dextran group, particularly 5–20 min after injection.

DISCUSSION

In addition to the studies noted above, other investigators have also examined the effects of a dextran adjuvant on the duration of action and the absorption of local anaesthetic solutions.

In 1967, Chinn and Wirjoatmadja [11] observed that the addition of dextran in ulnar blocks prolonged objective anaesthesia by 10–20%. They proposed that this might result from the formation of a loose complex between the dextran macromolecules and the local anaesthetic.

Kaplan, Miller and Gallagher [12] used low molecular weight dextran (dextran 40) to supplement 0.75% bupivacaine in intercostal blocks. They found that the mean duration of action of this solution was approx. 36 h; when bupivacaine was administered alone it was less than 12 h.

Whereas previous investigators used only clinical criteria, more sophisticated animal experiments were performed in 1978 by Åberg, Friberger and Sydnes [13]. They demonstrated that the absorption of radioactive labelled mepivacaine was delayed by the addition of dextran; this was attributed to the formation of water-soluble complexes of dextran and the local anaesthetic. However, the authors could not confirm these results in tests involving dental infiltration anaesthesia. They concluded that this phenomenon was caused by poor diffusibility of the solution to its site of action within the alveolar process. They also reported that the addition of dextran reduced the acute toxicity (LD_{50}) of mepivacaine in mice after subcutaneous application, but not when administered by i.v. injection.

Other clinical trials and animal experiments have not provided conclusive results, or demonstrated any synergistic dextran effect [14–18]. It is worth noting that, in all these studies, low molecular weight dextran was used. However, other authors have found the combination to be effective [19]. Further investigations were performed using mixtures of dextran and local anaesthetic in different ratios [20], dextrans of high and low molecular weight [21–23] and solutions with various pH values. Some studies concluded that the effect of the addition of dextran was caused by increasing alkalization of the solution and that molecular weight was not an important factor [24, 25]. In a dialysis model, these authors were able to demonstrate that the addition of dextran did not reduce the elimination of bupivacaine [24]. Similar results were obtained by Scurlock and Curtiss [26]. Investigations of a Scandinavian group [27–30] did provide evidence for the activity of dextran when used to supplement prilocaine, but not bupivacaine. They, too, ascribed this effect to an increase in viscosity.

Ueda, Hirakawa and Mori [31, 32] demonstrated that dextran inhibited the absorption of adrenaline. Lignocaine increased the systemic concentrations of adrenaline, which the authors ascribed to the vasodilator effect of lignocaine, but it was possible to mitigate this effect by the addition of dextran. This study, however, was not performed during standardized anaesthesia; the observation period lasted only 30 min and the authors did not specify from which site blood samples were drawn for catecholamine analysis.

The present study was designed to investigate the effect of a dextran adjuvant on the absorption of a local anaesthetic solution under standardized clinical conditions over a longer observation period in patients during modified neurolept-anaesthesia. The simultaneous determination of adrenaline and lignocaine concentrations using lignocaine as an internal standard should provide reliable results with regard to patterns of absorption and length of time for which the active substance remains at the site of injection.

According to the plasma noradrenaline concentrations in both test groups and the concentrations of adrenaline and noradrenaline in the control group, surgical stress had no evident influence on the course of anaesthesia. Therefore the adrenaline concentrations recorded in the two test groups reflect the process of absorption at the site of injection.

The adrenaline concentrations exceed other results reported in the literature [33, 34], although there was no clinical evidence for intravascular injection.

The addition of 6% dextran to the lignocaine solution containing adrenaline caused a definite reduction in uptake of the catecholamine from its injection depot. This effect reduced the high initial concentrations and led to a prolonged, continuous absorption.

The dextran adjuvant had a similar effect on the uptake of lignocaine. The lignocaine concentrations were markedly reduced and extended over a long period without wide variations. Although the time course of clinical effects was not investigated in this study, it may be assumed that the delayed absorption of the solution is accompanied by a prolonged duration of action.

Under the conditions described here, the different absorption patterns of the two solutions had no obvious effect on mean arterial pressure. Comparable local anaesthesia in awake patients may lead to other results. Nevertheless, differences in heart rate were evident in the present study.

The following conclusions may be drawn regarding clinical practice:

(1) Because of its absorption-reducing action, the addition of dextran to adrenaline-containing solutions may protect against toxic systemic side effects of both adrenaline and lignocaine.

(2) This effect is of particular significance in patients with cardiovascular and endocrine disorders and in patients who are susceptible to convulsions.

(3) The dextran adjuvant may reduce toxicity resulting from administration of adrenaline-containing local anaesthetic solutions in patients during inhalation anaesthesia, especially with halothane.

(4) Since the local anaesthetic solution remains for a longer time at the site of injection, a prolonged duration of action may also be expected.

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INFUSION OF ATRACURIUM IN NEONATES, INFANTS AND CHILDREN

A Study of Dose Requirements

I. KALLI AND O. A. MERETOJA

SUMMARY

The doses of atracurium (by infusion) required to maintain steady-state (90–95%) neuromuscular block were assessed in 75 children aged 9 days to 17 yr during balanced anaesthesia. Following the intubating dose of atracurium 0.4 mg kg^{-1} and after the recovery of single twitch to 5–10% of control (monitored by evoked EMG of hypothenar muscle), an infusion of atracurium 0.5 mg kg^{-1} h^{-1} was started. In 22 of the patients this initial rate resulted in the desired steady state; 32 patients required one, and 21 required two or more adjustments in rate. The mean single twitch value at steady-state was 6.6±0.3% (SEM), which is equal to 93% neuromuscular block. The infusion requirement to maintain the steady state neuromuscular block in all paediatric patients more than 1 month old was constant (0.53±0.01 mg kg^{-1} h^{-1}). The infusion requirement of neonates up to 1 month old was 25% less (0.40±0.02 mg kg^{-1} h^{-1}; $P = 0.003$). A significant correlation ($n = 75$, $r = 0.76$, $P < 0.001$) was found between the infusion rate (mg m^{-2} h^{-1}) and the logarithm of the body surface area.

Atracurium, a non-depolarizing neuromuscular blocking agent with an intermediate duration of action, is decomposed spontaneously by Hofmann elimination and metabolized by non-specific esterases [1]. The main reasons for using atracurium during prolonged operations are: its elimination does not depend on renal or hepatic mechanisms, and there is little, if any, cumulation and only a minor risk of postoperative residual neuromuscular blockade [2, 3]. On account of the short elimination half-life of atracurium [4, 5], it is logical to give the drug by continuous infusion during long surgical procedures.

The aim of this study was to determine the doses of atracurium (given by infusion) required to maintain a steady 90–95% neuromuscular block in neonates, infants and children during balanced anaesthesia.

PATIENTS AND METHODS

Seventy-five patients (aged 9 days to 17 yr) undergoing elective operations were selected for the study and allocated to seven groups according to body weight (table I). The patients did not suffer from any disease, nor were they receiving medication known to influence neuromuscular transmission. The operations on the neonates ($n = 7$: aged less than 1 month) consisted of four orthopaedic and three urological procedures. The infants ($n = 17$; aged between 1 and 12 months) underwent two orthopaedic, three abdominal, 11 open heart operations and one closure of patent

TABLE I. *Patient characteristics (mean ± SEM). BW = body weight range of a patient group; BSA = body surface area* [6]

Group	BW range	n	Weight (kg)	BSA (m^2)	Age (yr)
1	< 5.0	11	4.2±0.2	0.25±0.01	0.3±0.1
2	< 7.0	10	5.8±0.2	0.32±0.01	0.6±0.1
3	< 10.0	12	8.4±0.3	0.41±0.01	1.3±0.1
4	< 15.0	10	12.6±0.5	0.55±0.02	2.8±0.4
5	< 20.0	11	16.9±0.5	0.71±0.02	6.1±0.4
6	< 30.0	10	24.1±0.9	0.93±0.03	8.2±0.5
7	> 30.0	11	44.1±3.8	1.38±0.08	13.3±0.8

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TABLE II. *Detailed information on the neonates* (n = 7) *up to 1 month old*

	Mean	Range
Gestational age (week)	40.5	39–42
Birth weight (kg)	3.9	3.3–4.6
APGAR score at 1 min	9	8–10
Age at operation (day)	17	9–30
Weight at operation (kg)	4.1	3.4–5.4

TABLE III. *Steady-state atracurium infusion requirement (mean ± SEM). **Statistically significant difference between infants under 5.0 kg* (n = *11) and the other children* (n = *64*): P = *0.01. ***Significant difference after* ANOVA *and the comparison between means (Bonferroni's correction) of group 1* v. *groups 3–7, group 2* v. *groups 6–7, group 3* v. *groups 6–7, group 4* v. *group 7*: P < *0.0015*

Group	mg kg^{-1} h^{-1}	mg m^{-2} h^{-1}
1	0.44 ± 0.04**	7.41 ± 0.71***
2	0.52 ± 0.04	9.65 ± 0.76***
3	0.53 ± 0.02	10.78 ± 0.30***
4	0.50 ± 0.03	11.44 ± 0.64***
5	0.52 ± 0.05	12.46 ± 1.13
6	0.54 ± 0.02	14.15 ± 0.58
7	0.56 ± 0.04	17.42 ± 1.27
P (ANOVA)	0.256	0.000

ductus arteriosus. The operations on the children ($n = 51$; older than 1 yr) consisted of nine orthopaedic, seven abdominal, 31 open heart and four vascular operations. The detailed information of the seven neonates is shown in table II.

The design of the study was approved by the Ethical Committee of the Children's Hospital, University of Helsinki. Premedication consisted of flunitrazepam 0.1 mg kg^{-1} by mouth (maximum dose 2.0 mg) for all but those patients who were less than 5 kg in body weight; they received 10 mg kg^{-1} of methohexitone per rectum. Premedication of the children weighing less than 15 kg was supplemented, when indicated, with the same dose of methohexitone. The induction of anaesthesia was carried out with fentanyl 3 μg kg^{-1}, thiopentone 1–2 mg kg^{-1} and nitrous oxide in oxygen (2:1).

To monitor the neuromuscular transmission by EMG, the stimulating surface electrodes were placed over the ulnar nerve near the wrist, and the recording electrodes on the hypothenar muscles. Following the induction of anaesthesia, supramaximal stimuli with trains of four (TOF) impulses at 20-s intervals were given (Relaxograph, Datex Oy, Helsinki, Finland). The evoked compound electromyogram was amplified, integrated and recorded on a thermal printer. After the calibration and baseline recording, atracurium 0.40 mg kg^{-1} was given and the trachea was intubated when the first twitch (T1) of the train-of-four was less than 10% of the calibration control value.

The infusion of atracurium 20 or 50 mg diluted in 100 ml of cold 5% glucose was commenced at a rate of 0.50 mg kg^{-1} h^{-1} (Ivac 700, Ivac Corp., San Diego, California) after the recovery of T1 to 5–10% of control. The infusion was adjusted gradually by increasing or decreasing its rate every 20–30 min to maintain the first twitch height between 5 and 10% of control. If there was a marked increase in the height of the single twitch, small bolus increments of atracurium were given to restore the neuromuscular block to the desired value before the infusion rate was increased. The individual steady-state infusion rate was judged to be that which maintained the neuromuscular block constant at 90–95% for at least 20 min. This final rate was calculated on the basis of both body weight (BW) and body surface area (BSA).

During anaesthesia, the end-tidal carbon dioxide concentration was maintained at 5.0–5.5% (Normocap, Datex Oy, Finland), and the core temperature at 35.5–37.0 °C. No inhalation anaesthetics were used at any time during the study, but fentanyl was administered in doses of 1–2 μg kg^{-1} as required. There was no notable blood loss during the recording period. The conditions were the same for the patients undergoing open heart surgery, in whom the study was carried out before the period of cardiopulmonary bypass.

Statistical differences between the groups were assessed using analysis of variance (ANOVA), with the Welch modification in cases of unequal variances [7], and the *t* test (Bonferroni's correction in comparison between group means after ANOVA). Linear regression analysis was used in appropriate instances. The values are expressed as mean ± SEM. Statistical difference was considered significant at $P < 0.05$.

RESULTS

In 22 patients, the desired steady-state degree of neuromuscular block was achieved with the initial infusion rate. Thirty-two patients required one and 21 patients two or more adjustments in rate before steady-state neuromuscular block was achieved and maintained. The mean duration of the recordings was 122 ± 13 min, and the mean duration of the steady-state period was 60 ± 5 min. Once constant neuromuscular block was reached, the mean T1 level was 6.6 ± 0.3 %, which was equal to 93 % neuromuscular block.

The requirements at steady state in the seven patient groups are presented in table III. The infusion rate based on body weight was lower in patients weighing less than 5 kg than in heavier patients (0.44 mg kg^{-1} h^{-1} *v.* 0.53 mg kg^{-1} h^{-1}) ($P < 0.01$). The infusion rate in patients heavier than 5 kg was constant when calculated on the basis of body weight (table III).

The infusion rates in neonates, infants and children are shown in table IV. The table shows that the infusion rate in neonates (0.40 mg kg^{-1} h^{-1}) was 25 % lower than the infusion rate in older patients ($P = 0.004$).

TABLE IV. *Patients and infusion rates in different age groups (mean and SEM). †Significant difference between neonates and children : P = 0.004. **Significant difference between all three groups after ANOVA and the comparison between group means (Bonferroni's correction is used in both) : P < 0.017*

	n	Age (yr)	mg kg^{-1} h^{-1}	mg m^{-2} h^{-1}
Neonates	7	0.05 ± 0.01	0.40 ± 0.02†	6.75 ± 0.48**
Infants	17	0.61 ± 0.06	0.52 ± 0.03	9.72 ± 0.57**
Children	51	6.61 ± 0.64	0.53 ± 0.01	13.32 ± 0.53**
P (ANOVA)			0.01	0.000

The infusion rate based on body surface area increased in proportion to the growth of the patient (table III). There was a statistically significant correlation ($r = 0.76$, $P < 0.001$) between the logarithm of BSA and the infusion rate based on BSA (fig. 1).

DISCUSSION

The results of this study demonstrated that the infusion rate of atracurium needed to maintain a steady 90–95 % neuromuscular block remained constant when calculated on a body weight basis, in paediatric patients with body weights greater than 5 kg.

The mean infusion rate in infants and children (0.53 mg kg^{-1} h^{-1}) was similar to that recorded by Brandom and colleagues [8] and Goudsouzian and co-workers [9], who studied the infusion requirements of children between 2 and 10 years of age and between 1 and 10 years of age, respectively. The requirement was the same in adult surgical patients [10, 11]. The greater interindividual variation of the infusion requirements (range 0.30–0.88 mg kg^{-1} h^{-1} in our study) is a typical finding. Thus a neuromuscular monitoring device should be used to ensure success of the infusion technique.

The requirement of atracurium by infusion in neonates has not been studied previously. We found that the neonates required a mean infusion rate of 0.40 mg kg^{-1} h^{-1}, which was 25 % less than

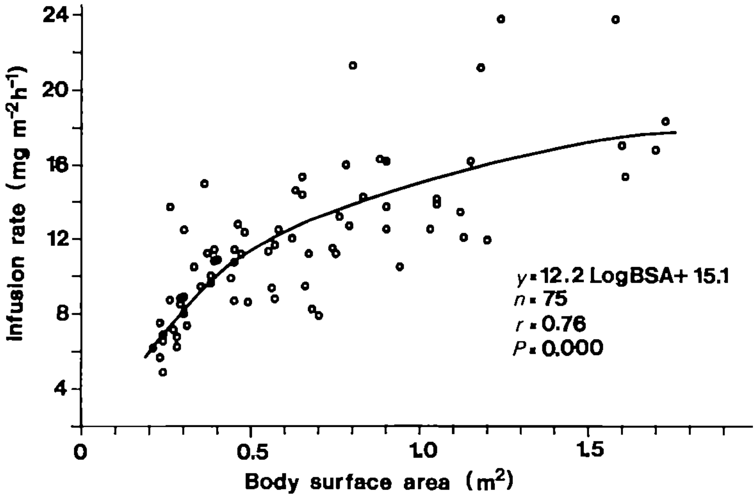

FIG. 1. Atracurium infusion requirement based on body surface area increases in proportion to growth. A statistically significant correlation between the infusion rate (mg m^{-2} h^{-1}) and the logarithm of body surface area (BSA) is shown.

the infusion requirements of older infants and children.

The lower infusion requirement can be explained by the immaturity of the neuromuscular junction and muscle contraction, which is known to exist for 2–3 months postnatally [12, 13]. The influence of the distribution volume of atracurium at different ages, and the possibility of delayed elimination in neonates is only speculative, and has still to be tested in pharmacokinetic studies in the newborn. The results of the present study are in agreement with our previous study, which showed that the recovery index (time elapsed between the single twitch recovery 25% and 75%) during spontaneous recovery after a bolus dose of atracurium was significantly longer in patients younger than 3 months than in older infants and children [14]. Possibly atracurium, like tubocurarine [15], is effective at a lower plasma concentration in neonates than in older paediatric patients.

When the infusion requirement was calculated on the basis of body surface area, a logarithmic correlation was found between the BSA of the patient and the infusion rate (mg m^{-2} h^{-1}). The infusion requirements found by Brandom and colleagues [8] for the group of children between 2 and 10 years of age and by d'Hollander and associates [10] in adults, fit well the regression obtained in the present study. However, the calculation of the infusion rate needed by an individual patient is, for practical reasons, more complex if calculated on the basis of BSA instead of body weight.

In conclusion, the present clinical study demonstrates that the requirements of atracurium (by infusion) in paediatric patients older than 1 month is constant when calculated on a body weight basis (mg kg^{-1} h^{-1}). The infusion requirement of neonates was found to be 25% lower.

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HAEMODYNAMIC EFFECTS OF DILTIAZEM DURING FENTANYL–NITROUS OXIDE ANAESTHESIA†

An In Vivo *Study in the Dog*

R. M. GRIFFIN, I. DIMICH, R. JURADO AND J. A. KAPLAN

SUMMARY

The haemodynamic effects of diltiazem were studied in six dogs during fentanyl–nitrous oxide (in oxygen) anaesthesia. A bolus of diltiazem 300 µg kg⁻¹ was given, followed by infusions at 30, 60 and 90 µg kg⁻¹ min⁻¹ which produced plasma diltiazem concentrations of 392±30, 908±54 and 1483±134 ng ml⁻¹, respectively. Diltiazem significantly reduced systemic vascular resistance index, mean arterial pressure, heart rate and PR interval. The decrease in afterload increased cardiac index, since there was little change in myocardial contractility (LV dP/dt). Five dogs developed second degree atrio-ventricular (AV) block in association with the highest dose. Administration of calcium chloride 20 mg kg⁻¹ did not reverse the haemodynamic or electrophysiological effects of diltiazem. Isoprenaline increased heart rate and restored sinus rhythm in four dogs with AV block.

Diltiazem is a calcium channel blocking agent which is used in oral form for the treatment of variant [1] and classic stable angina [2]. Diltiazem is also available in a water soluble, non-light sensitive preparation and may be a useful drug for the management of hypertension, myocardial ischaemia and arrhythmia, in the peri-operative period. Several studies in animals [3–5] have described the use of diltiazem i.v. in association with volatile anaesthetic agents. However, patients with coronary artery disease who may benefit from intraoperative diltiazem therapy are likely to receive fentanyl as part or all of the anaesthetic technique. This study was designed to investigate the cardiovascular effects produced with different plasma concentrations of diltiazem during fentanyl–nitrous oxide anaesthesia.

METHODS

Six unpremedicated mongrel dogs weighing 22.2±0.65 kg (mean±SEM) were anaesthetized with sodium thiopentone 20 mg kg^{-1} i.v. The trachea was intubated and ventilation was controlled with a constant volume ventilator using a mixture of 50% nitrous oxide and oxygen. Ventilatory rate and tidal volume were adjusted to maintain an arterial carbon dioxide tension of 4.7–5.3 kPa. An initial bolus of fentanyl 150 µg kg^{-1} was given followed by a continuous infusion of fentanyl 1.5 µg kg^{-1} min^{-1}. Pancuronium was given to ensure muscle paralysis. Oesophageal temperature was maintained between 37 and 39 °C with a warming mattress placed under the dog. Normovolaemia was maintained with a continuous infusion of lactated Ringer's solution 5–10 ml kg^{-1} h^{-1} via a femoral vein. Electrocardiographic needle electrodes were placed on the limbs for continuous recording of heart rate and rhythm. Intermittent recording of the ECG at 50 mm s^{-1} enabled determination of the PR interval. A 14-gauge polyethylene cannula (Intramedic) was threaded into a femoral artery to measure aortic pressure, and to permit intermittent blood sampling for blood-gas analysis (Corning Blood-Gas Analyser Model 165). A 7-French gauge thermodilution catheter was placed, via a femoral vein, in the pulmonary artery.

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Pulmonary artery pressure was monitored continuously and wedge pressure (PCWP) measured intermittently. Cardiac output was measured in triplicate (thermodilution) using an American Edwards Laboratories cardiac output computer (model 9520A). The heart was exposed through a median sternotomy and a catheter with a microtip pressure sensor (Millar Instruments, Inc., Model PC471), inserted into the left ventricle. Limb lead II of the electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), left ventricular pressure and electrically derived left ventricular contractile force (LV dP/dt) were displayed continuously on a Hewlett–Packard (model 7754B) four-channel oscillograph and recorded on a Hewlett–Packard (model 7755A) polygraph. Cardiac index (CI), stroke volume index (SVI), systemic and pulmonary vascular resistance indices (SVRI, PVRI) and left and right ventricular stroke work indices (LVSWI, RVSWI) were calculated using standard formulae.

Control measurements were taken 30 min after all instrumentation had been completed and repeated every 10 min until stable. An i.v. bolus of diltiazem 300 μg kg^{-1} was given over 2 min and the infusion of the lowest dose of diltiazem started. Diltiazem was administered at three infusion rates: 30 μg kg^{-1} min^{-1} (D_1), 60 μg kg^{-1} min^{-1} (D_2) and 90 μg kg^{-1} min^{-1} (D_3). Each infusion period lasted for 30 min. Haemodynamic measurements were obtained 2 min after the bolus and, subsequently, at 5, 15 and 30 min during each infusion of diltiazem. Arterial blood samples were taken for the measurement of blood-gas tensions, the serum concentrations of sodium, potassium, total calcium and the haematocrit at the end of each infusion period. Blood for determination of plasma concentration of diltiazem was taken 2 min after the bolus and at the end of each infusion period. Plasma diltiazem and desacetyldiltiazem were measured by high pressure liquid chromatography. After the final infusion of diltiazem (D_3), calcium chloride 20 mg kg^{-1} was given to each dog and measurements repeated 1 min later. Thereafter, each dog received isoprenaline 0.1 mg in 5% dextrose 100 ml as a continuous infusion of 5 μg min^{-1}. Haemodynamic measurements were obtained after 5 min.

TABLE I. *Summary of haemodynamic results (mean ± SEM) during infusion of diltiazem 30 μg kg^{-1} min^{-1} (D_1), 60 μg kg^{-1} min^{-1} (D_2) and 90 μg kg^{-1} min^{-1} (D_3); after calcium chloride (C) and isoprenaline infusion (I). HR = heart rate; PR = PR interval; MAP = mean arterial pressure; PCWP = mean pulmonary arterial wedge pressure; MPAP = mean pulmonary arterial pressure; RAP = right atrial pressure; CI = cardiac index; SVI = stroke volume index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; LVSWI = left ventricular stroke work index; RVSWI = right ventricular stroke work index; LV dP/dt = derived left ventricular contractile force.* *P < 0.05 *compared with control*; †P < 0.05 *for C compared with* D_3; ‡P < 0.05 *for I compared with C*

	Time from bolus of diltiazem (min) and stage in study						
	0 Control	2 D1	30 D1	60 D2	90 D3	91 C	96 I
HR (beat min^{-1})	109±6.1	139±14.0	116±11.7	111±10.4	90±13.0*	73±11.8	99±3.34‡
PR (ms)	120±0	130±6	190±26*	213±21*	220±28*	220±22	208±23
MAP (mm Hg)	105±7.3	82±5.5*	91±4.9*	80±3.6*	74±2.53*	75±3.12	72±3.54
PCWP (mm Hg)	11.5±0.76	11.6±0.88	12.8±1.13	14.3±0.80	15.1±1.10	15.2±1.39	15.6±2.29
MPAP (mm Hg)	16.1±1.32	19.0±2.03	19.5±1.78	21.6±2.07	22.5±2.02	21.6±2.9	22.8±1.39
RAP (mm Hg)	9.0±1.23	9.3±1.72	9.6±1.25	10.5±1.52	11.6±1.47	12.6±1.96	11.8±2.0
CI (litre min^{-1} m^{-2})	2.40±0.20	3.89±0.88	4.04±0.88*	4.67±0.95*	4.93±0.89*	5.35±1.08	5.52±0.64
SVI (ml m^{-2})	22.6±3.06	27.9±4.82	34.1±4.71	40.6±5.24*	54.5±4.74*	76.9±6.16†	55.4±5.65‡
SVRI (dyn s cm^{-5} m^{-2})	3249±257	1685±164*	1830±207*	1399±208*	1138±148*	1071±129	906±85
PVRI (dyn s cm^{-5} m^{-2})	161±34	170±36	150±29	143±37	125±22	93±17	107±23
LVSWI (g m m^{-2})	29.2±5.27	28.1±6.82	36.9±6.41	37.1±6.1	43.9±4.3	64.9±5.4	43.5±6.3
RVSWI (g m m^{-2})	2.19±0.35	4.01±1.27	4.86±1.23	6.76±1.89	8.57±1.91	10.0±3.78	8.7±2.62
LV dP/dt (mm Hg s^{-1})	1886±217	1733±256	1800±282	1750±268	1783±175	2940±820	2080±177
Plasma diltiazem (ng ml^{-1})		363±73	392±30	908±54	1483±134		

Repeated-measures analysis of variance with Bonferroni's correction was used to search for significant changes for each haemodynamic variable. Variables for which significance was found had subsequent measurements for each time point compared with control values using Fisher's least significant difference procedure. $P < 0.05$ was regarded as statistically significant.

RESULTS

The haemodynamic results and plasma concentrations of diltiazem are summarized in table I. MAP and SVRI were significantly reduced 2 min following the bolus injection of diltiazem (fig. 1). With increasing doses of diltiazem, SVRI was progressively reduced, reaching 35% of the control value at the end of D_3. CI showed a progressive increase with the infusion of diltiazem, which became significant at the end of D_1. Minimal depression of myocardial contractility (LV dP/dt) was observed. PCWP and LVSWI showed moderate increases with each infusion of diltiazem. HR increased following the bolus of diltiazem, but then decreased gradually to be significantly less than the control value during D_3 (fig. 2). PR was significantly prolonged 5 min after the administration of diltiazem (fig. 2).

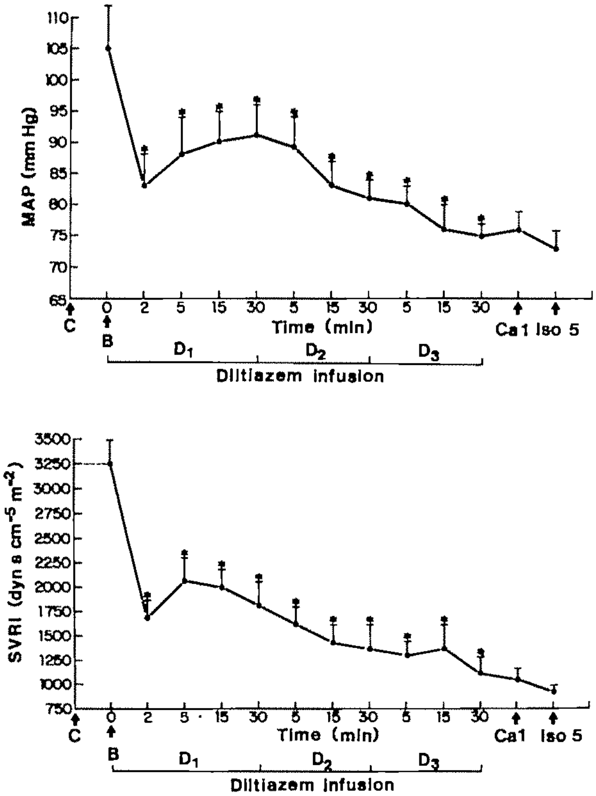

FIG. 1. Changes in mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) during infusion of diltiazem at 30 μg kg^{-1} min^{-1} (D_1), 60 μg^{-1} min^{-1} (D_2) and 90 μg kg^{-1} min^{-1} (D_3), 1 min after calcium chloride (Cal) and 5 min after isoprenaline infusion (Iso5). C = Control; B = bolus. $^*P < 0.05$ compared with control.

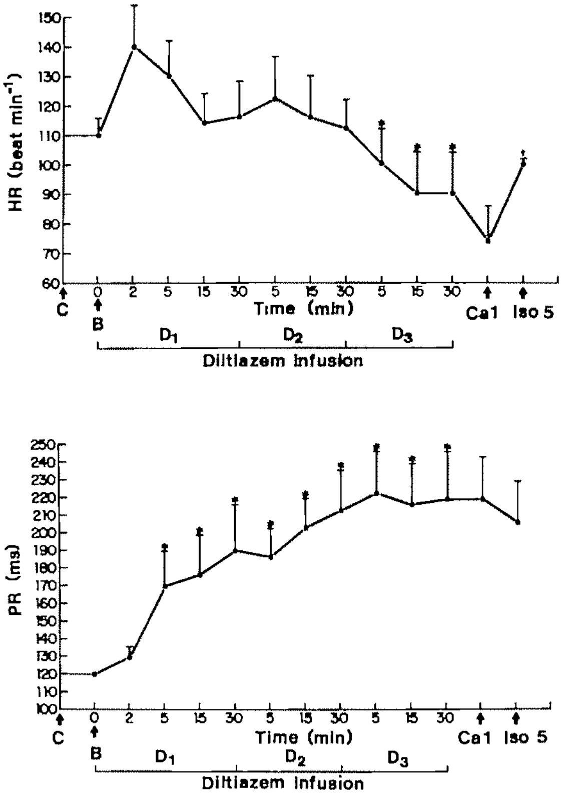

FIG. 2. Changes in heart rate (HR) and PR interval (PR) during infusion of diltiazem at 30 μg kg^{-1} min^{-1} (D_1), 60 μg kg^{-1} min^{-1} (D_2) and 90 μg kg^{-1} min^{-1} (D_3); 1 min after calcium chloride (Cal) and 5 min after isoprenaline infusion (Iso5). C = Control; B = bolus. $^*P < 0.05$ compared with control; $^\dagger P < 0.05$ for (Iso5) compared with (Cal).

Five dogs developed first degree atrioventricular (AV) block, three of these during D_1. All five dogs subsequently became established in second degree AV block, one during D_1, two during D_2 and two during D_3. In addition, two dogs had episodes of slow junctional rhythm. Figure 3 shows the development of all these arrhythmias in one dog, in association with the increasing plasma concentrations of diltiazem.

Calcium chloride significantly increased SVI,

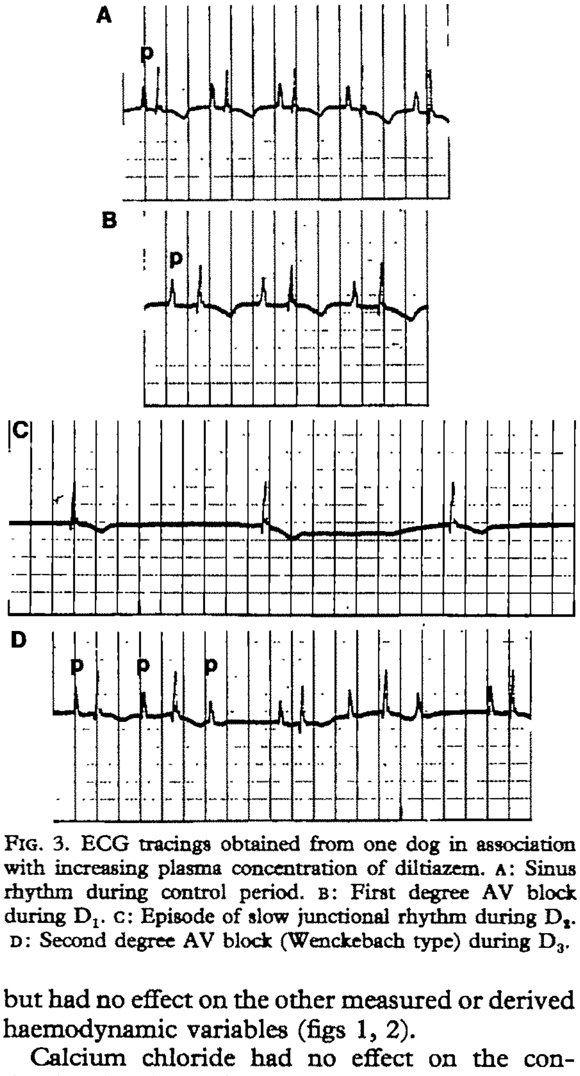

FIG. 3. ECG tracings obtained from one dog in association with increasing plasma concentration of diltiazem. A: Sinus rhythm during control period. B: First degree AV block during D_1. C: Episode of slow junctional rhythm during D_2. D: Second degree AV block (Wenckebach type) during D_3.

but had no effect on the other measured or derived haemodynamic variables (figs 1, 2).

Calcium chloride had no effect on the conduction block produced by diltiazem. However, the infusion of isoprenaline increased HR significantly and restored sinus rhythm in four out of the five dogs with AV block.

DISCUSSION

The net haemodynamic effects of calcium channel blockade in the intact animal are determined by the balance between the direct pharmacodynamic actions on the heart and peripheral circulation, their interaction and the degree of reflex sympathetic response which these elicit [6]. In the present study, the predominant haemodynamic effect of diltiazem during fentanyl–nitrous oxide (in oxygen) anaesthesia was a profound reduction in peripheral vascular resistance. The increase in cardiac output and the systemic hypotension were related to the decrease in afterload rather than any direct myocardial depression, since LV dP/dt was unaffected. The increase in heart rate seen after the bolus of diltiazem was indicative of an initial reflex sympathetic response to the acute reduction in peripheral resistance. However, as the dose increased, the direct negative chronotropic effect of diltiazem overcame this and produced a progressive decrease in heart rate.

Previous animal studies have found that the relative preponderance of haemodynamic and electrophysiological effects of diltiazem are dependent upon the plasma concentration. In dogs under barbiturate anaesthesia, solely electrophysiological effects were produced at (low) serum concentrations of 100–300 ng ml^{-1}, whereas much higher values (800–1800 ng ml^{-1}) were required to produce haemodynamic effects [7]. In a comparative study of calcium channel blockers in pigs anaesthetized with 1 MAC halothane [4], diltiazem was given until the mean arterial pressure had decreased 25–30 % from control values. The mean diltiazem plasma concentration measured at this point was 1650 ng ml^{-1}. Hypotension was secondary to a reduction in myocardial contractility, since systemic vascular resistance was unaffected, although LV dP/dt and cardiac index were reduced by 50 % and 42 %, respectively. In dogs anaesthetized with 1.5 % end-tidal isoflurane and given diltiazem [5], the only significant haemodynamic changes observed were depression of LV dP/dt and increases in left and right filling pressures. The lower plasma diltiazem concentrations (50–400 ng ml^{-1}) were insufficient to produce any changes in MAP. In accordance with the study of Kates and colleagues [4], there was no decrease in SVR with diltiazem. The use of a vasodilating anaesthetic may explain the lack of further vasodilatation produced by diltiazem, in comparison with the greater effect of diltiazem on SVRI and MAP during fentanyl–nitrous oxide anaesthesia. In the present study, plasma diltiazem concentrations of 300–400 ng ml^{-1} produced significant hypotension without any evidence of myocardial depression. In contrast, significant myocardial depression has been observed when diltiazem was administered during inhalation anaesthesia in animals. Therefore, in dogs, the mechanism of diltiazem-induced hypotension during fentanyl–nitrous oxide anaesthesia appears to be different from that produced in combination with volatile agents. To the extent that animal studies can be extrapolated to humans, the use of low-dose diltiazem by infusion in the absence of volatile agents may usefully produce a combination of a decrease in afterload, and an increase in cardiac index, with little change in heart rate.

The potential use of diltiazem in clinical anaesthesia may be limited by adverse electrophysiological effects, which occur at plasma concentrations necessary to achieve haemodynamic changes. Second degree AV block and junctional escape rhythm at plasma concentrations of less than 300 ng ml^{-1} have been reported during enflurane [8] and isoflurane [5] anaesthesia in dogs. In the present study, during fentanyl–nitrous oxide anaesthesia, second degree AV block was not observed consistently until relatively high plasma diltiazem concentrations were achieved (greater than 400 ng ml^{-1}). By this time, there were significant effects on SVRI and, consequently, MAP. Further investigation of lower plasma diltiazem concentrations in combination with fentanyl-based anaesthesia may be warranted to determine the optimum plasma concentration with which to achieve the desired haemodynamic effect, with minimal changes in intracardiac conduction time.

In animals, calcium chloride has been shown to counteract the haemodynamic, but not the electrophysiological, effects of calcium channel blockade with verapamil [9]. Calcium chloride was given to reverse the haemodynamic changes produced by diltiazem. Although myocardial contractility was increased, the systemic arterial vasodilatation and hypotension induced by diltiazem were not antagonized by calcium chloride. This is in agreement with the findings of Kates and colleagues [4] who observed a slight decrease in SVR after the administration of calcium chloride to pigs given diltiazem during halothane anaesthesia. An alpha-adrenergic agonist drug such as phenylephrine may be more effective for correction of the peripheral vasodilator effects of prolonged administration of calcium channel blockers.

No effect of calcium chloride was observed on the prolonged AV conduction produced by diltiazem, confirming the results of previous studies [4, 9]. Reves [10] has proposed the use of AV sequential pacing for severe impairment of AV conduction, secondary to calcium channel blockade. However, a pharmacological approach for the correction of conduction block may be simpler and equally effective. Isoprenaline, a beta-agonist, was successful in re-establishing normal conduction in the majority of these dogs. To the extent that this animal study is relevant to clinical anaesthetic practice, isoprenaline should be considered as the drug of choice for the treatment of severe conduction defects produced by diltiazem during fentanyl–nitrous oxide anaesthesia.

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CARDIOVASCULAR EFFECTS OF DILTIAZEM IN THE DOG

K. SKARVAN AND H.-J. PRIEBE

Despite improvements in the anaesthetic management of patients with coronary artery disease, the occurrence of myocardial ischaemia is still a serious threat during the perioperative period. Ischaemia is usually associated with tachycardia, arterial hypertension, increased wall tension or coronary vasoconstriction [1]. Consequently, the ideal treatment should decrease arterial and ventricular filling pressures, and heart rate, and decrease coronary artery tone without having any adverse effects on myocardial contractility and conduction. Diltiazem is one of the recently-introduced calcium entry blockers available for i.v. use in man. In its oral form it is highly effective in the management of angina pectoris [2]. When administered i.v. to conscious subjects, it is a potent coronary and systemic vasodilator without evidence of untoward effects on heart rate or myocardial contractility [3, 4]. In addition, it possesses antiarrhythmic properties [5, 6], and protects the myocardium from ischaemic and reperfusion injury [7, 8]. Thus it may be well suited for the treatment of perioperative myocardial ischaemia. However, the efficacy and safety of diltiazem during anaesthesia remain to be determined as hypotension, bradycardia and abnormalities of conduction have been reported after i.v. administration in anaesthetized man, and anaesthetized animals [9, 10].

The aim of this study was to investigate the effects of bolus injections and constant infusions of diltiazem on the systemic, pulmonary and coronary circulations, on global and regional left (LV) and right ventricular (RV) function, and on the ECG during neuroleptanaesthesia. Administration of nitroglycerin (TNG) before and after the administration of diltiazem served to assess the effects of anaesthesia and of diltiazem on baroreceptor function.

SUMMARY

The effects of two bolus injections (0.2 mg kg^{-1}) and two infusion rates (0.2 mg min^{-1} and 0.4 mg min^{-1}) of diltiazem on global and regional left (LV) and right ventricular (RV) performance (ultrasonic dimension technique), on coronary (electromagnetic flow meters) and systemic haemodynamics, and on electrophysiology (PR, QRS, QT_c intervals) were studied in eight open-chest dogs anaesthetized with droperidol and fentanyl. The two bolus injections of diltiazem resulted in plasma concentrations of 688 ± 115 and 650 ± 85 ng ml^{-1} (means ± SE), respectively, and caused substantial decreases in systemic and coronary vascular resistances, and in aortic pressure, and increases in LV segment shortening, stroke volume and aortic flow. Electrophysiological variables were little affected. At the low infusion rate (plasma concentration 140 ± 23 ng ml^{-1}) coronary and systemic vasodilatation occurred, but global and regional RV and LV performance were little affected. PR interval increased by 15%. At the higher infusion rate (plasma concentration 282 ± 33 ng ml^{-1}) coronary and systemic vasodilatation were maintained. Aortic pressure decreased slightly. Whereas LV end-diastolic and end-systolic dimensions remained unchanged, they increased in the RV. In addition, the PR interval increased by 35%, and three animals developed atrioventricular block type I. The data indicate that diltiazem is a potent coronary and systemic vasodilator with little effect on global RV and LV performance. However, at a higher infusion rate RV dimensions clearly tend to increase, and conduction abnormalities develop.

METHODS

Instrumentation

Eight mongrel dogs of either sex weighing between 27 and 33 kg received fentanyl

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0.04 mg kg^{-1} and a large dose of droperidol (2 mg kg^{-1}) i.m. 1 h before the induction of anaesthesia. After this premedication the dogs became heavily sedated, recumbent, and did not resist the placement of a peripheral venous cannula. Anaesthesia was induced with small incremental doses of pentobarbitone i.v. up to a maximum total of 10 mg kg^{-1} and then maintained with continuous infusions of pentobarbitone 1 mg kg^{-1} h^{-1} i.v., and fentanyl 20 µg kg^{-1} h^{-1} i.v. Additional bolus doses of fentanyl 500 µg were given i.v. whenever increases in heart rate and arterial pressure, or movements, indicated a decrease in the depth of anaesthesia. The trachea was intubated and controlled ventilation (Harvard constant-volume ventilator, Harvard Apparatus Co., South Natick, MA) facilitated by a continuous infusion of pancuronium 0.04 mg kg^{-1} h^{-1} i.v. Tidal volume was set at 15 ml kg^{-1}. Ventilatory rates and inspired oxygen concentrations were adjusted to maintain the arterial carbon dioxide tension (Pa_{CO_2}) between 4 and 5.3 kPa and the arterial oxygen tension (Pa_{O_2}) between 20 and 46.7 kPa. Positive end-expiratory pressure (2 cm H_2O) was applied to prevent major airway collapse in the open-chest animals. Sodium bicarbonate was administered if the calculated base deficit exceeded 5 mmol litre^{-1}. All dogs were in the supine position and placed on a heating element incorporated in the operating table. Body temperature was monitored continuously by the thermistor of a flow-directed thermodilution catheter (Edwards Laboratory, Santa Ana, CA, Model 93-132-5F) inserted through the right jugular vein into the pulmonary artery. All animals received 4–6 ml kg^{-1} h^{-1} of physiological saline i.v.

Catheter-tip manometers (6F, Millar Instruments Inc, Houston, TX) were advanced into the ascending aorta just above the aortic valve, and into the left and right ventricles. The catheter-tip manometers were prewarmed in a water bath at 37 °C for several hours, and they were calibrated simultaneously and immediately before insertion. Calibration was performed by actuating a switch incorporated in the connection cable that produced an electrical output corresponding to a pressure of 100 mm Hg. Baseline stability of the high-fidelity signals was verified repeatedly during the experiment by superimposing the manometer-derived pressures on those derived either from the separate fluid-filled catheter in the aortic arch, or from the fluid-filled lumina incorporated in the RV and LV catheter-tip manometers using Statham transducers (P23 ID). The chest was entered through a median sternotomy and the heart was suspended in a pericardial cradle. Precalibrated electromagnetic flow probes (Stölzer Messtechnik, Waldkirch, West Germany) of appropriate sizes (to ensure a snug fit) were placed around the ascending aorta, the right coronary artery (RCA) approximately 1–2 cm distal to its origin, and the left anterior descending coronary artery (LAD) distal to its first large diagonal branch. The flow probes were connected to flow meters with incorporated non-occlusive zero (Hellige Co., Freiburg i. Br., West Germany).

Regional myocardial function

Regional myocardial performance was evaluated by sonomicrometry [11, 12]. Pairs of piezoelectric crystals (5 MHz, 1.5–2.0 mm diameter) were inserted into the subendocardium of the inflow (longitudinal direction) and outflow tract (transverse direction) of the RV (RVIT and RVOT). A third pair was inserted in an equatorial plane into the subendocardium of the LV distal to the first or second diagonal branch of the LAD. Care was taken to place the crystals in the inflow tract of the RV and those in the apical region of the LV within the areas supplied by the RCA and LAD, respectively. Myocardial segment lengths (SL) between each pair of crystals were determined at end-diastole (SL_{ed}) and at the time of maximal shortening during systole (SL_{sys}). From these values, percent segment shortening during systole (ΔSL) was derived [$\Delta SL\ (\%) = (SL_{ed} - SL_{sys})/SL_{ed} \times 100$]. End-diastole was defined as the beginning of the sharp upslope in the expanded LV and RV pressure tracings, and end-systole by the dicrotic notch in the aortic pressure signal as derived from the catheter-tip manometers. Analysis of aortic flow and pressure signals in several animals showed that zero aortic flow and the dicrotic notch occurred within 40 ms of each other. The ultrasonic signals were also assessed visually for qualitative changes such as akinesis, paradoxical systolic segment lengthening or postsystolic segment shortening.

Haemodynamic measurements

A multichannel recorder (Hellige Co., Freiburg i. Br., West Germany) was used for the continuous recording of all signals. LV dP/dt was derived from LV high-fidelity signals using operational amplifiers connected to a differentiator (Hellige

Co., Freiburg i. Br., West Germany). Right (RVSW) and left ventricular stroke work (LVSW), and stroke volume (SV) were derived from standard formulae. Systemic (SVR), pulmonary (PVR), and right (CVR_R) and left anterior descending (CVR_{LAD}) coronary artery vascular resistances were derived from the following formulae:

$$\text{SVR (dyn s cm}^{-5}) = \frac{\text{MAoP (mm Hg)} - \text{RVEDP (mm Hg)}}{\text{AoF min}} \times 80$$

$$\text{PVR (dyn s cm}^{-5}) = \frac{\overline{P\text{PA}}\text{ (mm Hg)} - \text{LVEDP (mm Hg)}}{\text{AoF (litre min}^{-1})} \times 80$$

$$\text{CVR}_R\text{ (kdyn s cm}^{-5}) = \frac{\text{MAoP (mm Hg)} - \text{RVEDP (mm Hg)}}{\text{CBF}_R\text{ (ml min}^{-1})} \times 80$$

$$\text{CVR}_{LAD}\text{ (kdyn s cm}^{-5}) = \frac{\text{AoP}_d\text{ (mm Hg)} - \text{LVEDP (mm Hg)}}{\text{CBF}_{LAD}\text{ (ml min}^{-1})} \times 80$$

where MAoP = mean aortic pressure, RVEDP = right ventricular end-diastolic pressure, AoF = mean aortic flow, $\overline{P\text{PA}}$ = mean pulmonary artery pressure, LVEDP = left ventricular end-diastolic pressure, CBF_R = mean right coronary artery blood flow, AoP_d = end-diastolic aortic pressure, and CBF_{LAD} = mean left anterior descending coronary artery blood flow. Heart rate (HR) was derived from the R–R intervals of an extremity ECG.

Electrocardiographic (ECG) measurements

Lead II of the ECG was recorded continuously and analysed for evidence of arrhythmias and conduction abnormalities. Five consecutive cardiac cycles recorded at end-expiration at a chart speed of 100 mm s^{-1} were used for the measurements of the PR, QRS and QT intervals. QT_c intervals were calculated according to the formula:

$$QT_c = \frac{QT}{\sqrt{RR}}$$

where RR = cycle length of ECG (s).

Experimental programme

After sternotomy, and approximately 2 h before the start of the experiment, pentobarbitone was discontinued. Any adjustments in ventilation, acid–base status, depth of anaesthesia, and fluid administration were made no later than 30 min before the start of the definitive study.

Hydrophilized diltiazem hydrochloride dissolved in distilled water was freshly added to 0.9% sodium chloride to yield concentrations of 1 mg ml^{-1} and 0.4 mg ml^{-1} for bolus injection and continuous infusion, respectively. Commercially available i.v. nitroglycerin (Trinitrosan, Merck) 5 mg ml^{-1} was diluted in 0.9% sodium chloride to obtain a concentration of 50 μg ml^{-1}.

Following control readings a bolus dose of TNG 5 μg kg^{-1} was administered. After the return of all measured variables to control values (C), a bolus dose of diltiazem 0.2 mg kg^{-1} was administered. This was followed by a continuous infusion (0.2 mg min^{-1}) which was maintained for 30 min. Immediately after the measurements, a further i.v. bolus of diltiazem 0.2 mg kg^{-1} was given, and the infusion rate was doubled to 0.4 mg min^{-1} and maintained at this rate for 30 min. Finally, an additional bolus of TNG 5 μg kg^{-1} was administered. Measurements following the bolus injections of TNG and diltiazem were made at the time of the lowest AoP which occurred within 1 min of injection. Measurements during the infusions were made during steady-state conditions at the end of each of the two 30-min infusion periods of diltiazem (0.2 mg min^{-1} = $D1_{inf}$; 0.4 mg min^{-1} = $D2_{inf}$).

Arterial blood was sampled during C and at the end of each diltiazem infusion period for determinations of haematocrit (Hct) (Microcentrifuge Compur, Munich, West Germany, Model M1100), arterial blood-gas tensions and arterial pH (Instrumentation Laboratory, Lexington, MA, Model 613), and plasma concentrations of diltiazem. Additional measurements of diltiazem plasma concentrations were obtained following the two bolus injections. Diltiazem was assayed by electron-capture gas–liquid chromatography. As internal standard the butyryl analogue of diltiazem was used. This method has an overall sensitivity of less than 5 ng/ml of plasma [13].

Statistical analysis

The data were analysed statistically by Friedman's statistic. If this indicated statistical significance, the Wilcoxon signed-rank test was used to isolate the significant difference between treatments by making paired comparisons [14]. A P value of < 0.05 was considered significant.

TABLE I. *Effects of diltiazem on systemic haemodynamics and left ventricular function (mean ± SE). C = control; $D1_{bol}$ and $D2_{bol}$ = first and second i.v. bolus injection of diltiazem 0.2 mg kg^{-1}; $D1_{inf}$ and $D2_{inf}$ = infusions of diltiazem 0.2 mg min^{-1} and 0.4 mg min^{-1}, respectively. $LVSL_{ed}$ = left ventricular (LV) end-diastolic segment length; $LVSL_{sys}$ = LV systolic segment length; ΔLVSL = LV systolic segment shortening; LVEDP = LV end-diastolic pressure; MAoP = mean aortic pressure; HR = heart rate; AoF = aortic flow; SV = stroke volume; LVSW = LV stroke work; SVR = systemic vascular resistance.* †$P < 0.05$ *when compared with C;* *$P < 0.05$ *when compared with preceding value;* §$P < 0.05$ *when $D2_{inf}$ compared with $D1_{inf}$*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
$LVSL_{ed}$ (mm)	9.2±0.4	9.1±0.4	9.2±0.2	9.4±0.3	9.4±0.3
$LVSL_{sys}$ (mm)	6.3±0.3	5.8±0.4†	6.1±0.3	5.8±0.3	6.3±0.2
ΔLVSL (%)	31.2±2.7	35.4±3.8†	33.1±2.7	38.7±3.5†*	32.5±2.9
LVEDP (mm Hg)	5.9±0.4	5.7±0.4	5.8±0.4	5.9±0.6	6.2±0.7
MAoP (mm Hg)	94±3	75±4†	92±4*	75±4†*	88±2†*
LV dP/dt_{max} (mm Hg s^{-1})	2492±163	2521±183	2531±172	2598±222	2492±185
HR (beat min^{-1})	94±6	103±6†	97±6*	97±4	94±6
AoF (litre min^{-1})	2.0±0.2	2.5±0.2	2.3±0.2	2.6±0.3†*	2.3±0.3
SV (ml $beat^{-1}$)	22±2	24±2†	24±3	26±3†*	25±3†
LVSW (g m)	27±3	23±3†	28±4*	26±4	28±4
SVR (dyn s cm^{-5})	3649±177	2349±78†	3261±152†*	2294±127†*	3127±292†*

TABLE II. *Effects of diltiazem on pulmonary haemodynamics and right ventricular function (mean ± SE). $RVITSL_{ed}$ = right ventricular (RV) inflow tract (IT) end-diastolic segment length; $RVISTL_{sys}$ = RVIT systolic segment length; ΔRVITSL = RVIT systolic segment shortening; $RVOTSL_{ed}$ = RV outflow tract (OT) end-diastolic segment length; $RVOTSL_{sys}$ = RVOT systolic segment length; ΔRVOTSL = RVOT systolic segment shortening; RVEDP = RV end-diastolic pressure; RVSP = RV systolic pressure;* $P\overline{PA}$ *= mean pulmonary artery pressure; RVSW = RV stroke work; PVR = pulmonary vascular resistance. (See table I for further abbreviations)*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
$RVITSL_{ed}$ (mm)	10.3±0.6	10.7±0.6†	10.4±0.6	10.9±0.7†*	10.8±0.7†§
$RVITSL_{sys}$ (mm)	8.1±0.6	8.3±0.6	8.2±0.6	8.4±0.7†	8.4±0.7†
ΔRVITSL (%)	22.0±1.4	22.9±2.0	21.6±1.9	23.3±1.9	22.7±1.7
$RVOTSL_{ed}$ (mm)	10.5±0.8	10.9±1.0†	10.9±1.0†	11.3±1.0†*	11.3±0.9†
$RVOTSL_{sys}$ (mm)	8.0±0.7	8.2±0.8	8.2±0.7	8.4±0.8†	8.4±0.7†
ΔRVOTSL (%)	24.1±1.7	25.7±1.5	25.1±1.5	25.6±1.1	25.7±1.6
RVEDP (mm Hg)	3.6±0.3	4.1±0.4	3.9±0.3	4.5±0.4†*	3.9±0.3
RVSP (mm Hg)	29±2	30±1	30±2	31±2	29±2
$\overline{PPA}$ (mm Hg)	13±1	14±1	13±1	14±1	14±1
RVSW (g m)	2.9±0.6	3.4±0.7†	3.0±0.5	3.6±0.6†*	3.5±0.6§
PVR (dyn s cm^{-5})	274±31	275±25	274±33	267±26	280±34

RESULTS

Effects of bolus injections of diltiazem on systemic and pulmonary haemodynamics, and on RV and LV function (tables I and II)

The two bolus injections of diltiazem resulted in plasma concentrations of 688 ± 115 ($D1_{bol}$) and 650 ± 85 ng ml^{-1} ($D2_{bol}$), respectively. The first bolus injection ($D1_{bol}$) caused a decrease in MAoP accompanied by increases in HR and AoF, and a decrease in SVR and LVSW. LVEDP and LV dP/dt_{max} remained unchanged. $LVSL_{sys}$ decreased, and ΔLVSL increased. In contrast to the response of the LV and the systemic circulation, $RVIT_{ed}$ and $RVOT_{ed}$ increased; ΔSL did not change. RV systolic pressure (RVSP), $P\overline{AP}$ and RVSW tended to increase, and PVR remained unchanged.

In contrast to $D1_{bol}$, the second bolus injection ($D2_{bol}$) given at the end of the lower-dose infusion had no effect on HR, despite a similar decrease in MAoP. It caused additional increases in $RVITSL_{sys}$ and $RVOTSL_{sys}$, and in RVEDP. All other effects were comparable to $D1_{bol}$.

TABLE III. *Effects of diltiazem on left and right coronary haemodynamics (mean ± SE). CBF$_{LAD}$ = mean left anterior descending coronary artery blood flow; CBF$_{R}$ = mean right coronary artery blood flow. (See table I for further abbreviations)*

Variable	C	D1$_{bol}$	D1$_{inf}$	D2$_{bol}$	D2$_{inf}$
CBF$_{LAD}$ (ml min^{-1})	27±3	43±7†	32±4†*	43±6†*	36±5†*§
CBF$_{R}$ (ml min^{-1})	14±2	25±3†	18±2†*	26±3†*	21±2†*§
CVR$_{LAD}$ (kdyn s cm^{-5})	241±23	115±17†	194±23†*	111±15†*	171±24†*§
CVR$_{R}$ (kdyn s cm^{-5})	530±40	257±36†	406±37†*	242±36†*	343±39†*
CBF$_{LAD}$/HR (µl beat^{-1})	286±32	412±53†	330±37†*	442±55†*	380±51†§
CBF$_{R}$/HR (µl beat^{-1})	154±16	237±26†	187±19†*	267±31†*	222±18†*§
CBF$_{LAD}$/AoF·100 (%)	1.32±0.13	1.74±0.21†	1.51±0.21	1.76±0.23†	1.69±0.27§
CBF$_{R}$/AoF·100 (%)	0.72±0.06	1.01±0.11†	0.86±0.11†*	1.07±0.13†*	0.99±0.13†

There were no qualitative changes in sonomicrometry signals—such as akinesis or paradoxical systolic segment lengthening.

Effects of bolus injections of diltiazem on coronary haemodynamics (table III)

Following D1$_{bol}$ there were pronounced increases in coronary blood flow (CBF), in CBF per heart beat (CBF/HR) and in CBF expressed as a fraction of AoF (CBF/AoF), and a decrease in CVR. These responses were clearly blunted during D2$_{bol}$.

Effects of the infusion of diltiazem on systemic and pulmonary haemodynamics, and on LV and RV function (tables I and II)

The two infusion rates of diltiazem resulted in plasma concentrations of 140±23 ng ml^{-1} (D1$_{inf}$) and 282±33 ng ml^{-1} (D2$_{inf}$), respectively. Except for a slight decrease in SVR, the low infusion rate (D1$_{inf}$) had no significant effects on systemic haemodynamics or LV function. At the higher infusion rate (D2$_{inf}$) there was a small (7%) decrease in MAoP, and increases (13%) in SV and AoF. However, when compared with each other there were no differences between D1$_{inf}$ and D2$_{inf}$. Except for an isolated increase in RVOTSL$_{ed}$, D1$_{inf}$ had no significant effect on RV function or on the pulmonary circulation. At the higher infusion rate (D2$_{inf}$), however, end-diastolic and end-systolic dimensions of RVIT and RVOT, and RVSW increased without changes in segment shortening. $\overline{PAP}$ and PVR remained unchanged throughout. As with the bolus doses, there were no qualitative changes in the sonomicrometry signals.

Effects of the infusion of diltiazem on left and right coronary haemodynamics (table III)

During both infusion periods there were marked increases in CBF, in the amount of coronary blood flow per heart beat (CBF/HR) and in the ratio of CBF and AoF (CBF/AoF), accompanied by similar decreases in CVR.

Correlation between plasma concentrations of diltiazem and haemodynamic effects

There were significant negative correlations between the plasma concentrations of diltiazem and changes in MAoP ($r = -0.62$, $P < 0.01$), SVR ($r = -0.65$, $P < 0.01$), CVR$_{LAD}$ ($r = -0.58$, $P < 0.01$) and CVR$_{R}$ ($r = -0.38$, $P < 0.05$).

Effects of diltiazem on cardiac rhythm and electrophysiological variables (table IV)

QRS and QT$_{c}$ intervals remained unchanged throughout. During the infusions and following the second bolus injection, the PR interval increased. Three of the eight animals developed second degree atrioventricular block type I (Wenckebach) during the infusion of diltiazem at the higher rate.

Effects of TNG (table V)

The two bolus injections of TNG administered either before (TNG$_{1}$) or after (TNG$_{2}$) the second diltiazem infusion resulted in similar decreases (30%) in MAoP and similar increases (20–25%) in HR.

Changes in pHa, Pa_{O_2}, Pa_{CO_2}, Hct and temperature were minimal throughout the experiment (table VI).

TABLE IV. *Effects of diltiazem on electrocardiographic variables (mean ± SE). (See table I for further abbreviations)*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
PR (s)	0.14±0.01	0.13±0.01	0.16±0.01†*	0.15±0.01†	0.19±0.02†*
QRS (s)	0.08±0.01	0.07±0.01	0.07±0.01	0.07±0.01	0.07±0.01
QT_c (s)	0.33±0.01	0.34±0.01	0.32±0.01	0.32±0.01	0.33±0.01

TABLE V. *Effect of nitroglycerin-induced hypotension on heart rate before and after diltiazem (mean ± SE). TNG_1, TNG_2 = nitroglycerin (TNG) 5-µg kg^{-1} bolus administered before (TNG_1) and after (TNG_2) diltiazem infusion ($D2_{inf}$). *P < 0.05 when compared with the preceding value. (See table I for further abbreviations)*

Variable	C	TNG_1	$D2_{inf}$	TNG_2
MAoP (mm Hg)	96±3	68±4*	88±2	63±3*
HR (beat min^{-1})	91±7	117±6*	94±9	114±4*

TABLE VI. *Effects of experimental procedure on general homeostasis (mean ± SE). (See table I for further abbreviations)*

Variable	C	$D1_{inf}$	$D2_{inf}$
pHa	7.37±0.01	7.37±0.01	7.37±0.01
Pa_{O_2} (kPa)	33.1±2	31.6±2.53	31.2±2.93*
Pa_{CO_2} (kPa)	5.1±0.13	4.9±0.13†	4.8±0.13†
Hct (%)	35±1	37±1†	38±1†
Temp. (°C)	37.6±0.2	37.6±0.2	37.6±0.2

DISCUSSION

The purpose of this study was to examine the effects of i.v. administration of diltiazem on the cardiovascular system during neuroleptanaesthesia.

Diltiazem i.v. at clinically relevant plasma concentrations caused substantial systemic and coronary vasodilatation, and it enhanced LV pump function. At the same time, however, diltiazem caused dose-dependent prolongation of atrioventricular conduction. There were important differences between the effects of the bolus injections and the infusions of diltiazem, and differences between the effects on RV and LV function and on the different circulations.

Critique of methods

The design of the study simulated the clinical situation in which diltiazem is given to patients undergoing open heart surgery. In addition, the second bolus injection of diltiazem, given on top of the lower rate infusion, approximated the clinical situation in which those patients receiving diltiazem before operation receive an additional dose during the operative procedure.

Clinically relevant plasma concentrations of diltiazem were achieved during both infusion rates [15, 16]. The bolus injections resulted in considerably higher values. The plasma concentrations after the second bolus injection were lower than expected and statistically not different from those found after the first bolus. At present we have no explanation for this finding.

The cardiovascular effects of a calcium entry blocker given during operation depend on the interactions with the anaesthetic drugs used and on the baseline conditions of the circulation. In this study the anaesthesia was based on droperidol given in a large dose i.m. before induction of anaesthesia, and on fentanyl given as a continuous infusion and supplemented with additional bolus doses when required. While adverse interactions have been described between diltiazem and inhalation anaesthetic agents [10, 17, 18], the effects of diltiazem during i.v. anaesthesia have not been studied as yet. The baseline haemodynamic status was characterized by a normal heart rate, a normal arterial pressure and a slightly decreased aortic flow. This haemodynamic pattern closely resembles the clinical situation following sternotomy and pericardiotomy [19]. The discontinuation of pentobarbitone 2 h before the measurements should have minimized myocardial depression [20], but, with regard to the long elimination half-time of pentobarbitone, a potential for later interactions cannot be totally excluded. In addition, negative inotropic influences may be more pronounced in the open-chest than in the closed-chest animal [21]. Nevertheless, the lower baseline aortic flow appears to be primarily the result of the opening of the chest, positive pressure ventilation, and reductions in venous return and ventricular filling.

On the other hand, normal heart rates and arterial pressures during the control period indicate that there was no inappropriate sympathoadrenergic stimulation. The responsiveness of the autonomic nervous system, however, was well maintained, as demonstrated by the baroreflex-mediated tachycardia after nitroglycerin.

Effects of diltiazem on systemic and pulmonary circulations

Diltiazem proved to be a potent systemic vasodilator. This is in accordance with previous studies [3, 22]. Except during the low-dose infusion, the reductions in SVR were accompanied by a decrease in AoP. In contrast, diltiazem did not alter PVR and $\bar{P}$AP. Similar results have been reported previously [9, 23–25].

Coronary circulation

Diltiazem proved to be a potent coronary vasodilator. A direct vasodilatory effect appeared to dominate, since CBF and CBF/HR increased in the presence of decreases in coronary perfusion pressure and evidence of reduced myocardial oxygen demand.

The changes in the coronary circulation were more pronounced than the respective changes in the systemic circulation (fig. 1). This would indicate that diltiazem is an even more powerful coronary, than systemic, vasodilator. This has previously been suggested [26]. The effects of diltiazem on the coronary circulation appear to vary with the baseline anaesthetic. In contrast to the results of this study, CVR did not change in dogs anaesthetized by isoflurane or enflurane [17, 18].

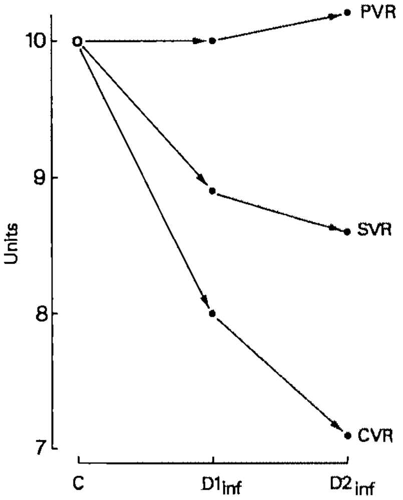

FIG. 1. Changes in pulmonary (PVR), systemic (SVR), and left anterior descending coronary artery vascular resistances (CVR) from control (C) to the first infusion rate of diltiazem ($\mathrm{D1}_{\mathrm{inf}}$) and from $\mathrm{D1}_{\mathrm{inf}}$ to the second infusion rate of diltiazem ($\mathrm{D2}_{\mathrm{inf}}$). Mean values during control have all been standardized to an initial value of 10. There was a significant difference ($P < 0.05$) between the changes of PVR and CVR. SVR tended ($P < 0.1$) to respond less than CVR and more than PVR to the infusion of diltiazem.

Diltiazem and ventricular performance

Diltiazem had no adverse effects on global right (RVSP, RVSW) or left (AoF, SV, LVSW) ventricular performance. This is in agreement with results of previous studies which have shown that, in therapeutic doses, diltiazem has little effect on inotropy in intact animals or in awake man [3, 27]. However, when looking at our data in greater detail, differences in the response to diltiazem between RV and LV, and in the effects of bolus injections and infusions become apparent. Segment shortening and stroke volume increased following the bolus injections, but no such effects were noted during the low-dose infusion, and were less prominent during the high-dose infusion. There are several possible explanations for this difference. First, the decreases in SVR were more pronounced following the bolus injections. At constant preload, a decrease in SVR tends to increase the volume ejected from and returning to the LV [28]. This can be viewed as an upward shift of the LV function curve [29] and could explain the improved LV pump function.

Second, because of the greater decrease in MAoP following the bolus injections, there might have been a more pronounced baroreflex-mediated increase in sympathetic outflow, resulting in increased contractility. However, the findings of an unchanged LV dP/dt, and an unchanged HR, following the second bolus injection do not support such a mechanism.

Third, during the infusions of diltiazem some myocardial depression might have outweighed the beneficial effects of a decrease in afterload on LV function. A direct negative inotropic effect of diltiazem has been demonstrated *in vitro* [27].

The fact that no such effect was noted following the bolus injections, despite considerably higher plasma concentrations, can best be explained by a greater baroreflex-mediated increase in sympathetic tone or the counterbalancing effect of a greater decrease in LV afterload.

The LV end-diastolic dimension and pressure remained unchanged throughout. The systemic

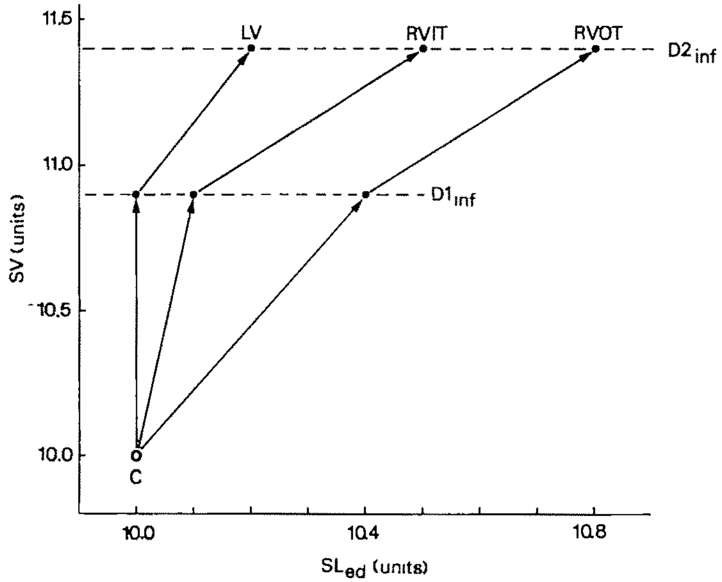

FIG. 2. Plot of end-diastolic segment lengths (SL_{ed}) *v.* stroke volume (SV). Mean values during control (C) have all been standardized to an initial value of 10. The arrows indicate the directional changes from control to the first infusion rate of diltiazem ($D1_{inf}$), and from $D1_{inf}$ to the second infusion rate of diltiazem ($D2_{inf}$). Note the differences in slopes of the SV–SL_{ed} relationship between left and right ventricle. There is a trend ($P < 0.1$) to right- and downward shift of the SV–SL_{ed} relationship in the RVIT and RVOT when compared with LV.

vasodilatation, however, usually shifts the diastolic pressure–volume curve of the LV downwards [30]. Correspondingly, in the presence of an unchanged LV end-distolic dimension (and volume), the LVEDP should have decreased.

Several factors may be responsible for the absence of any changes in LVEDP. First, the increase in flow associated with systemic vasodilatation will increase the diastolic filling rate and, consequently, also the viscous component of the LV compliance [31]. Second, profound coronary vasodilatation may increase the LV wall volume relative to LV chamber volume [32]. Third, an increase in RV end-diastolic dimensions may decrease the LV distensibility by the mechanism of ventricular interdependence [33]. All three factors would counterbalance the effects of an acute reduction in afterload on the LV pressure–volume relation by shifting it in the opposite direction. The net result would be an unchanged LVEDP (as observed), despite substantial changes in LV afterload.

Compared with the LV, the RV operated under clearly different loading conditions. Indices of RV preload (end-diastolic dimensions and pressure) increased and indices of RV afterload ($\overline{PAP}$, PVR) remained unchanged. In contrast to the LV, the increase in output was associated with an increase in preload (fig. 2). It remains to be determined whether this represents an upward shift along the same ventricular function curve, or a right- and downward shift to a different ventricular function curve, indicating myocardial depression. Differences in RV and LV regional myocardial performance are probably related to the different effects of diltiazem on the afterload of the RV (unchanged) and on that of the LV (reduced). This could have potentially important clinical implications for patients receiving diltiazem in the presence of increased RV afterload.

In contrast to the preservation of global RV and LV function during fentanyl anaesthesia noted in this study, in the presence of volatile anaesthetics, diltiazem has been shown to be a potent myocardial depressant [10, 17, 18]. This might have been the result of absence of afterload reduction, underlying myocardial depression caused by inhalation anaesthetics or impaired baroreceptor reactivity. In the present study, the increase in HR following the bolus injections of nitroglycerin indicated that baroreceptor function was preserved, even during the high-dose infusion of diltiazem. It is, therefore, to be expected that the net haemodynamic response to diltiazem will depend on the kind of application (bolus *v.* infusion), the state of wakefulness (awake *v.* anaesthetized), and the baseline anaesthetic (i.v. *v.* inhalation).

Diltiazem and cardiac rate and rhythm

We observed a dose-dependent increase in the duration of the PR interval during the infusion of diltiazem. This observation is in agreement with other experimental and human studies: diltiazem has a profound effect on sinus and atrioventricular pacemakers, both nodes being slow calcium channel dependent tissues [34].

Except for a 10% increase following the first bolus injection, HR remained unaffected. *In vitro*, diltiazem exhibits direct dose-dependent negative chronotropic effects [27, 34]. In awake subjects, however, HR tends to decrease minimally [3, 35], and in conscious animals there may even be a dose-dependent increase in HR [27, 36]. As the increase in HR following the first bolus injection of diltiazem indicates, the suppressant effect of diltiazem on the sinoatrial node *in vitro* is apparently modified *in vivo* by the reflex increase in sympathetic tone which results from the decrease in arterial pressure [34]. Moreover, pancuronium was used in this study and might antagonize the negative chronotropic effect of diltiazem [37]. As suggested by the absence of any increase in HR in response to the second bolus injection, at high plasma concentrations direct negative chronotropic effects may suppress the reflex increase in HR.

Diltiazem caused progressive alterations in electrophysiological variables. During both infusions the PR intervals increased in a dose-dependent manner and, during the high infusion rate, three animals developed atrioventricular block. This clearly reflects impaired atrioventricular conduction. However, the development of atrioventricular block might be limited by the facilitating effect of pancuronium on atrioventricular conduction [37]. Similar increases in PR interval and similar arrhythmias at similar plasma concentrations have been reported previously [6, 38, 39]. This suppressant effect on the atrioventricular node is also seen clinically [34], but it is less pronounced and, at times, occurs only at considerably higher plasma concentrations [35]. On the other hand, during isoflurane anaesthesia in dogs, PR intervals increased at considerably lower plasma diltiazem concentrations [17]. Despite five-fold higher plasma concentrations after the bolus injections (rather than during the infusion) PR intervals did not increase following either bolus injection. This might have been because of a greater reflex increase in sympathetic tone in response to the more pronounced decrease in arterial pressure.

The durations of the QRS interval and QT_c remained unchanged throughout. This was to be expected because, in contrast to the slow calcium channel-dependent tissues of sinus and atrioventricular nodes, the His-Purkinje system and the ventricular muscle are fast channel-dependent tissues in which the inward current is not primarily carried by calcium ions. This is consistent with the finding of an unchanged ventricular muscle effective refractory period in anaesthetized animals at plasma concentrations which significantly depressed antrioventricular node function [38].

Clinical implications

Diltiazem proved to be a potent coronary and systemic vasodilator without adverse effects on heart rate and global pump function. Consequently, under similar clinical conditions (for example, open heart surgery during neuroleptanaesthesia), diltiazem might improve myocardial oxygen balance by decreasing oxygen demand and increasing oxygen supply. Our results were obtained in animals with presumed normal coronary arteries and myocardium, and the results cannot be extrapolated directly to patients with coronary artery disease. However, beneficial effects of diltiazem have been demonstrated in different types of experimental ischaemia [40–45]. These data indicate that diltiazem may be suitable for the treatment of perioperative ischaemia. Moreover, diltiazem has been shown to prevent sympathetically-mediated constriction of normal and diseased coronary arteries in man [46]. This effect may be important in preventing coronary vasoconstriction and myocardial ischaemia as a result of sympathetic stimulation during the perioperative period. However, some of the beneficial effects of diltiazem may be lost during the infusion of high doses as a result of the development of clinically relevant myocardial depression and abnormalities of conduction. Therefore, bolus injections of diltiazem might be preferable.

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EFFECTS OF LIGNOCAINE AND BUPIVACAINE ON REGIONAL MYOCARDIAL FUNCTION AND CORONARY BLOOD FLOW IN ANAESTHETIZED DOGS

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SUMMARY

Empirical i.v. doses of lignocaine or bupivacaine of equal local anaesthetic potency were administered to halothane-anaesthetized dogs. Both local anaesthetics caused the expected depression of global haemodynamic function. Regional myocardial systolic shortening was depressed similarly by both agents. Regional myocardial dysfunction, seen as post-systolic shortening, occurred to a similar extent with both lignocaine and bupivacaine. Coronary blood flow and coronary perfusion pressure were significantly correlated during the administration of lignocaine; bupivacaine had erratic effects on coronary blood flow and no correlation between coronary blood flow and coronary perfusion pressure was seen. These results suggest that regional myocardial dysfunction occurs with both local anaesthetics and does not account for the apparent increased cardiotoxicity of bupivacaine. Bupivacaine did, however, cause wider individual variations compared with lignocaine with respect to coronary blood flow.

Lignocaine and bupivacaine are used widely in association with techniques of extradural regional anaesthesia and i.v. regional anaesthesia [1,2]. However, after reports of severe cardiotoxicity associated with the apparent i.v. injection of bupivacaine [3,4], several investigators have reported that bupivacaine is more cardiotoxic than lignocaine [5–7], whereas others have not [8].

Regional myocardial function is a sensitive indicator of myocardial ischaemia [9]. For example, we have reported that the combination of volatile anaesthetics and the calcium channel blocker, verapamil, caused regional myocardial dysfunction (seen as post-systolic shortening (PSS)) in myocardium with normal coronary arteries [10,11]. As local anaesthetics alter sodium conductance and may disrupt calcium fluxes [1], we wondered whether the administration of lignocaine or bupivacaine i.v. would cause regional myocardial dysfunction, similar to that seen with verapamil, in the presence of a normal coronary circulation. We also examined whether the occurrence of asynchronous left ventricular wall motion could be related to the cardiotoxicity of the local anaesthetics.

MATERIAL AND METHODS

Twelve mongrel dogs (wt 17–33 kg) were premedicated with morphine sulphate 0.1 mg kg^{-1} and anaesthesia was induced with thiopentone 7 mg kg^{-1}. After intubation of the trachea, positive pressure ventilation was instituted at a rate of 12 b.p.m. and the tidal volume adjusted to maintain normocarbia, as measured by end-tidal infra-red analysis. Halothane (1.2 % inspired) was

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used to maintain anaesthesia throughout the study. A heating element incorporated into the operating table maintained body temperature between 36 and 38 °C, as measured by an oesophageal temperature probe.

The animal was placed in the right lateral decubitus position and a catheter inserted, via the femoral vein, into the inferior vena cava. An infusion of Hartmann's solution was started at a rate of 4 ml kg^{-1} h^{-1}. The left common carotid artery was exposed, and a stiff 8-French gauge (2.76 mm o.d.) cannula was inserted and advanced to within 1 cm of the aortic valve. This cannula was connected to a calibrated pressure transducer (Druck Ltd, Groby, Leicester, U.K.) for the measurement of systemic pressures and was also used for blood sampling. Lead II of the electrocardiogram was monitored throughout the experimental procedure.

A left thoracotomy was performed and the 4th and 5th ribs excised. The pericardium was opened and the aortic root dissected free of its fat pad. An appropriately-sized electromagnetic flow probe (Transflow 601, Skalar Medical, Delft, Holland) was placed around the aortic root for flow measurement. A stiff 8-French gauge (2.76 mm o.d.) cannula was inserted via the apical dimple into the left ventricle and attached to a calibrated pressure transducer (Druck Ltd, Groby, Leicester, U.K.) to obtain measurements of left ventricular pressure. A cannula was placed in the pulmonary artery via the pulmonary outflow tract to permit measurement of cardiac output (indocyanine green).

The left anterior descending coronary artery (LAD) was dissected free of the epicardium. Measurements of coronary blood flow were obtained using a 2-mm electromagnetic flow probe (Transflow 601, Skalar Medical, Delft, Holland) placed around the artery. An occluding snare was placed just distal to the flow probe to allow determinations of zero flow.

Measurements of myocardial segment length were obtained using three pairs of piezo-electric crystals inserted to the subendocardium of the apex, mid-wall and base of the heart. The apical tissue was supplied by the LAD and the basal region by the left circumflex coronary artery (LC). Data on myocardial segment length were, therefore, recorded from left ventricular tissue in territory supplied by the LAD (LAD segment), in the mid-wall area (INT segment), and in territory supplied by the LC (LC segment). The techniques of ultrasonic sonomicrometry have been described previously [12–14]. Briefly, as ultrasound travels at a constant speed of 1.56 mm μs^{-1} through cardiac tissue, continuous measurement of myocardial segment length can be obtained.

After completion of the surgery the preparation was allowed to stabilize for 1 h. During this time, arterial blood-gas tensions were determined and any required changes in ventilation or corrections to acid–base balance undertaken. Instruments were calibrated and left ventricular end-diastolic pressure (LVEDP) measured. Dextran 70 (average mol. wt 70000 daltons) was given as necessary to maintain an LVEDP of 5 mm Hg. A 30-min period following any intervention elapsed before the beginning of the definitive investigation.

Experimental programme

To examine the effects of lignocaine or bupivacaine, the dogs were randomly allocated to one of two groups. Group 1 received i.v. injections of lignocaine and group 2 i.v. bupivacaine. The doses of both local anaesthetic agents used encompass the body weight normalized range for human anaesthesia. Doses were not scaled to individual body weights within this range as body weight has been shown to be a poor predictor of local anaesthetic blood concentration [15]. The initial dose of lignocaine was 50 mg, and each subsequent dose was twice the preceding dose, yielding doses of 50 mg, 100 mg and 200 mg for the three injections given. Likewise, each dose of bupivacaine was twice the previous dose, after an initial injection of 12.5 mg to compensate for the fourfold greater anaesthetic potency of bupivacaine compared with lignocaine. This schedule yielded bupivacaine doses of 12.5 mg, 25 mg and 50 mg for the three injections. Before the first dose, a baseline set of measurements was recorded. To allow equilibration of drugs between heart and brain, samples for measurements of blood concentrations of drugs were taken 10 min after each injection. After the recording of data was complete, the next dose of local anaesthetic was administered.

Computation

At the conclusion of the study the LAD was cannulated and calibration of the LAD flow probe performed by injecting 5-ml aliquots of blood through the LAD cannula. After calibration, 5 ml of Evans blue was injected through the LAD cannula. The resulting area of stained myocardium, representing the territory supplied by the LAD, was separated from non-stained myocardium. The atria were removed and the stained ventricular myocardial fragments weighed, thus enabling LAD flow measurements to be normalized as ml min^{-1}/100 g of myocardium.

The data were recorded as hard copy analogue signals on a Mingograf 81 (Elema Schoenander, Stockholm, Sweden). The first derivative of left ventricular pressure (LV dP/dt) was recorded, and its peak value measured (LV dP/dt_{max}). Aortic flow was both differentiated, to obtain aortic blood acceleration, and integrated, to obtain stroke volume. For purposes of measuring regional function, the ends of systole and diastole were defined as the first positive deflection of LV dP/dt and the first point after systole when aortic flow returned to zero, respectively. End-diastolic and end-systolic lengths (EDL, ESL, respectively) were measured using a paper speed of 250 mm s^{-1} to ensure accurate determinations of end-systole and end-diastole.

Data from the hard copy recordings were digitized manually. These were then analysed on a VAX computer using SAS, a commercially available statistical analysis programme (SAS, Inc, Cary, N.C., U.S.A.).

Mean arterial pressure (MAP) was calculated from the systolic and diastolic systemic arterial pressures (SAP, DAP, respectively). Coronary perfusion pressure (CPP) was calculated in the conventional manner as the difference between DAP and LVEDP. Cardiac output (CO) was determined from heart rate (HR) and stroke volume obtained from the aortic flowmeter. Dye dilution curves using indocyanine green were performed to calibrate the aortic flowmeter. PR interval was determined from lead II of the electrocardiogram. Percentage changes from baseline values were determined for CPP, CBF, SAP, LV dP/dt_{max} and CO, with baseline values normalized to 100%.

Regional function was examined by calculating systolic shortening and post-systolic shortening. Systolic shortening (SS) was defined as EDL minus ESL, and expressed as a percentage of EDL to compensate for preload-induced changes in performance. Post-systolic shortening (PSS) was defined as the difference between ESL and the minimum segment length measured during diastole. This was expressed as a percentage of total segmental shortening to compensate for changes in inotropy. EDL was normalized to a baseline value of 10.0 mm to adjust for differences in absolute intercrystal distances between animals resulting from initial placement [14].

Results were analysed for statistical significance using two-way analysis of variance and Duncan's test. However, some variables, notably PSS, exhibited skewed distributions and were analysed by the non-parametric Friedman two-way analysis of variance and sign test, as appropriate. Unpaired Student's t tests were used for comparisons of normalized values between lignocaine and bupivacaine. Linear regression was performed on normalized CPP, CBF and regional function data. In all cases, $P < 0.05$ was considered significant.

TABLE I. *Global haemodynamic data (mean ± SEM) during baseline conditions and after administration of lignocaine 50 mg, 100 mg and 200 mg.* *$P < 0.05$ *v. baseline by two-way analysis of variance and Duncan's multiple range test.* †$P < 0.05$ *v. baseline by Friedman two-way analysis of variance and sign test*

	Baseline	50 mg	100 mg	200 mg
HR (beat min^{-1})	99 ± 5	108 ± 4	106 ± 6	104 ± 6
SAP (mm Hg)	106 ± 6	90 ± 5*	77 ± 4*	54 ± 5*
LVEDP (mm Hg)	6.5 ± 0.7	7.8 ± 0.8	10.0 ± 0.9*	10.0 ± 0.4*
CPP (mm Hg)	73 ± 5	63 ± 3*	48 ± 4*	29 ± 4*
LV dP/dt_{max} (mm Hg s^{-1})	1260 ± 110	890 ± 90*	660 ± 70*	410 ± 40*
CO (litre min^{-1})	1.97 ± 0.14	1.66 ± 0.10*	1.25 ± 0.13*	0.77 ± 0.11*
SVR (dyn s cm^{-5})	3725 ± 440	3815 ± 350	4270 ± 310	4680 ± 275*
CBF ($n = 5$) (ml 100 g^{-1} min^{-1})	30.4 ± 6.7	26.5 ± 5.6	22.9 ± 6.2†	11.6 ± 7.5†
PR interval (ms)	105 ± 3	101 ± 3	101 ± 4	116 ± 8*

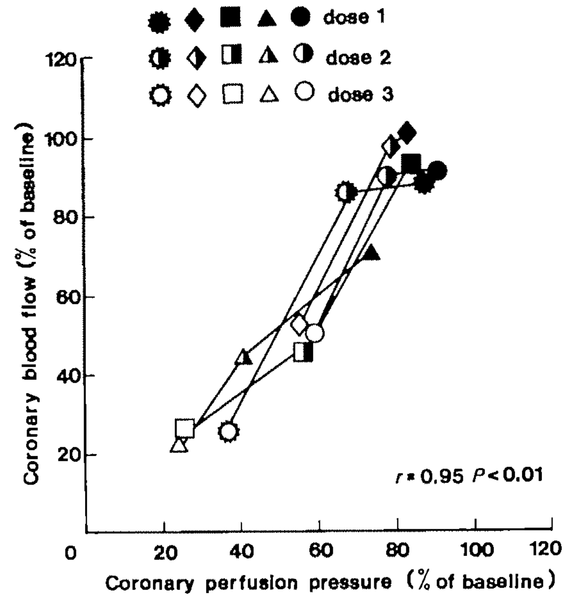

FIG. 1. Comparison between coronary blood flow (CBF) and coronary perfusion pressure (CPP) during baseline conditions and after three doses of lignocaine in five dogs. Data for CBF and CPP were normalized to baseline values of 100%. Each symbol represents results from an individual dog; the degree of shading indicates the lignocaine dose.

RESULTS

CBF measurements were performed in five dogs in both the lignocaine and bupivacaine groups. All other data for each local anaesthetic are from six dogs.

Lignocaine

The global haemodynamic data are presented in table I. Heart rate did not change as the dose of lignocaine increased. However, after each dose, SAP, CPP, CO and LV dP/dt_{max} decreased significantly. CBF decreased significantly at the two higher doses of lignocaine. PR interval increased significantly after the third dose of lignocaine. The average plasma drug concentrations were: 1.13 ± 0.09 μg ml^{-1} ($n = 6$) after dose 1, 2.89 ± 0.17 μg ml^{-1} ($n = 5$) after dose 2, and 6.92 ± 1.08 μg ml^{-1} ($n = 6$) after dose 3. The normalized CPP and CBF values were compared using linear regression and a significant correlation was shown between the two variables ($r = 0.95$, df $= 4$, $P < 0.01$). The slope of the resultant regression line was 1.06 ± 0.07 (fig. 1).

Data on regional function are shown in table II. Lignocaine caused a significant increase in EDL after the initial dose in the LC segment and significant increases in EDL with the second and third doses in all three myocardial segments. SS was significantly decreased with each dose of lignocaine in all three segments. Significant increases in PSS were apparent in the LAD territory after the second and third doses of lignocaine. Increases in PSS in the intermediate and LC segments achieved statistical significance only after the second dose.

Global haemodynamic and regional function data were normalized and expressed as a percentage of baseline values. Normalized CBF

TABLE II. *Regional myocardial function data (mean±SEM) during baseline conditions and after administration of lignocaine 50 mg, 100 mg and 200 mg.* *P < 0.05 v. *baseline by two-way analysis of variance and Duncan's test.* †P < 0.05 v. *baseline by Friedman two-way analysis of variance and sign test*

	Baseline	50 mg	100 mg	200 mg
LAD				
EDL (mm) (normalized)	10.0±0.0	10.3±0.0	10.5±0.2*	10.5±0.2*
SS (%)	20.2±2.2	13.4±2.5*	10.6±2.0*	9.4±1.0*
PSS (%)	4.6±2.3	23.5±10.6	29.0±10.5†	25.2±6.4†
INT				
EDL (mm) (normalized)	10.0±0.0	10.2±0.1	10.5±0.2*	10.7±0.2*
SS (%)	14.4±2.0	10.8±1.8*	8.6±1.5*	7.8±1.2*
PSS (%)	8.7±4.7	13.1±5.9	24.9±8.9	28.3±11.7
LC				
EDL (mm) (normalized)	10.0±0.0	10.2±0.1*	10.6±0.6*	10.8±0.2*
SS (%)	13.2±1.9	9.6±1.7*	7.2±1.3*	6.3±0.8*
PSS (%)	14.9±5.4	24.1±4.6	33.6±7.4†	20.2±6.0

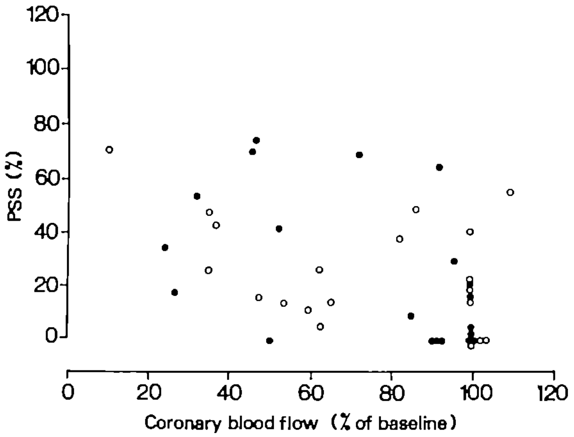

FIG. 2. Comparison between normalized coronary blood flow and absolute PSS values during baseline conditions and after three doses of lignocaine (●) or three doses of bupivacaine (○). Data were obtained from five dogs. No significant correlation was found (lignocaine: $r = 0.5$, df = 16, ns; bupivacaine: $r = 0.36$, df = 16, ns).

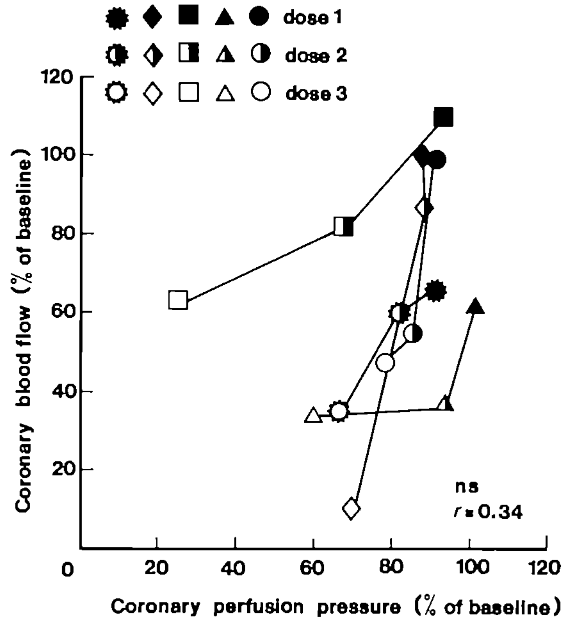

FIG. 3. Comparison between coronary blood flow (CBF) and coronary perfusion pressure (CPP) during baseline conditions and after three doses of bupivacaine in five dogs. Data for CBF and CPP were normalized to baseline values of 100%. Each symbol represents results from an individual dog; the degree of shading indicates the bupivacaine dose.

and normalized SS were tested for correlation and no significant relationship was found. Similarly, PSS was not significantly correlated with normalized CBF (fig. 2).

Bupivacaine

Table III shows the global haemodynamic data. The administration of bupivacaine did not alter heart rate significantly. The initial dose of bupivacaine did not result in any changes in SAP, CPP and CO, but the subsequent doses caused significant decreases in these variables. LV dP/dt_{max}, however, decreased significantly with each dose. CBF was decreased significantly at the two higher doses of bupivacaine. Owing to difficulties with storage and analysis of blood samples, several plasma bupivacaine concentrations were not determined. The average plasma drug concentrations were: 0.49 ± 0.07 μg ml^{-1} ($n = 4$) after dose 1, 0.68 ± 0.09 μg ml^{-1} ($n = 6$) after dose 2, and 1.22 ± 0.23 μg ml^{-1} ($n = 3$) after dose 3. PR interval was significantly increased after the second and third doses of bupivacaine. The normalized CPP and CBF values were

TABLE III. *Global haemodynamic data (mean ± SEM) during baseline conditions and after administration of bupivacaine 12.5 mg, 25 mg and 50 mg.* *$P < 0.05$ *v. baseline by two-way analysis of variance and Duncan's multiple range test.* †$P < 0.05$ *v. baseline by Friedman two-way analysis of variance and sign test*

	Baseline	12.5 mg	25 mg	50 mg
HR (beat min^{-1})	123 ± 11	123 ± 13	122 ± 11	120 ± 9
SAP (mm Hg)	105 ± 5	98 ± 4	90 ± 6*	75 ± 8*
LVEDP (mm Hg)	6.3 ± 0.6	7.0 ± 0.8	8.3 ± 1.1*	9.7 ± 1.0*
CPP (mm Hg)	73 ± 6	68 ± 4	62 ± 5*	46 ± 7*
LV dP/dt_{max} (mm Hg s^{-1})	1500 ± 150	1240 ± 140*	1020 ± 100*	680 ± 90*
CO (litre min^{-1})	2.67 ± 0.37	2.37 ± 0.35	1.96 ± 0.35*	1.44 ± 0.36*
SVR (dyn s cm^{-5})	2700 ± 555	3175 ± 530	3620 ± 635	4190 ± 865
CBF ($n = 5$) (ml 100 g^{-1} min^{-1})	29.9 ± 8.8	28.3 ± 11.0	20.5 ± 8.3†	13.3 ± 6.8†
PR interval (ms)	103 ± 8	111 ± 9	116 ± 8*	127 ± 10*

TABLE IV. *Regional myocardial function data (mean ± SEM) during baseline conditions and after administration of bupivacaine 12.5 mg, 25 mg and 50 mg.* *$P < 0.05$ v. *baseline by two-way analysis of variance and Duncan's test.* †$P < 0.05$ v. *baseline by Friedman two-way analysis of variance and sign test*

	Baseline	12.5 mg	25 mg	50 mg
LAD				
EDL (mm) (normalized)	10.0±0.0	10.1±0.1	10.3±0.1*	10.4±0.1*
SS (%)	17.2±1.3	13.8±1.1*	10.1±1.3*	8.4±1.8*
PSS (%)	10.0±5.0	24.4±5.3	29.0±6.6†	33.8±10.3†
INT				
EDL (mm) (normalized	10.0±0.0	10.1±0.1	10.3±0.1*	10.4±0.1*
SS (%)	12.5±2.2	9.5±2.2	8.2±1.5*	6.5±1.9*
PSS (%)	5.1±3.8	23.5±7.4†	25.6±6.6†	23.5±10.7
LC				
EDL (mm) (normalized)	10.0±0.0	10.6±0.1*	10.3±0.1*	10.4±0.1*
SS (%)	10.6±0.8	10.2±1.2	7.8±1.1*	6.6±1.2*
PSS (%)	10.3±4.1	14.7±3.7	16.4±5.7	23.8±9.9

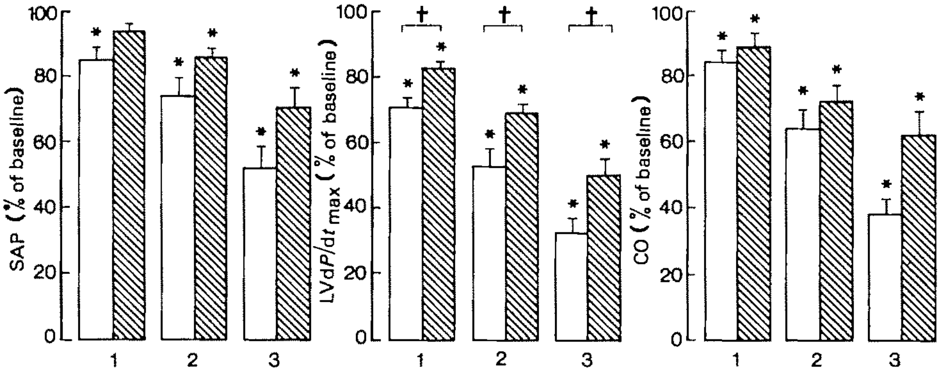

FIG. 4. The effects of lignocaine (open columns) and bupivacaine (cross-hatched columns) on three indices of global myocardial performance (SAP, LV dP/dt_{max}, and CO). All data were normalized to baseline values of 100%, and values obtained after local anaesthetic administration expressed as a percentage of baseline. 1 = Lignocaine 50 mg, bupivacaine 12.5 mg; 2 = lignocaine 100 mg, bupivacaine 25 mg; 3 = lignocaine 200 mg, bupivacaine 50 mg. Bars show the mean values, and error bars represent the SEM. *$P < 0.05$ *v.* baseline by two-way analysis of variance and Duncan's test; †$P < 0.05$ between lignocaine and bupivacaine values by unpaired Student's *t* test.

compared and no significant correlation was found ($r = 0.34$, df = 4, $P > 0.1$) (fig. 3).

Data on regional function are presented in table IV. Bupivacaine caused an increase in EDL in the LC segment with the initial dose, and caused increases in EDL in all segments with the second and third doses. SS was decreased in the LAD territory with the first dose and further injections caused a decrease in SS in all segments. PSS increased significantly in the LAD region after the second and third doses of bupivacaine and was increased in the intermediate territory after the first and second, but not the third, dose. No significant increase in PSS occurred in the LC segment.

Normalized CBF and normalized SS values were compared and no significant correlation found. The absolute PSS values had no significant correlation with normalized CBF (fig. 2).

Comparisons were made of normalized SAP, LV dP/dt_{max}, and CO data between lignocaine and bupivacaine (fig. 4). Each dose caused a significant decrease from baseline values of each variable, except for SAP with the first bupivacaine dose. Significant differences between the local anaesthetics occurred solely in LV dP/dt_{max}, and

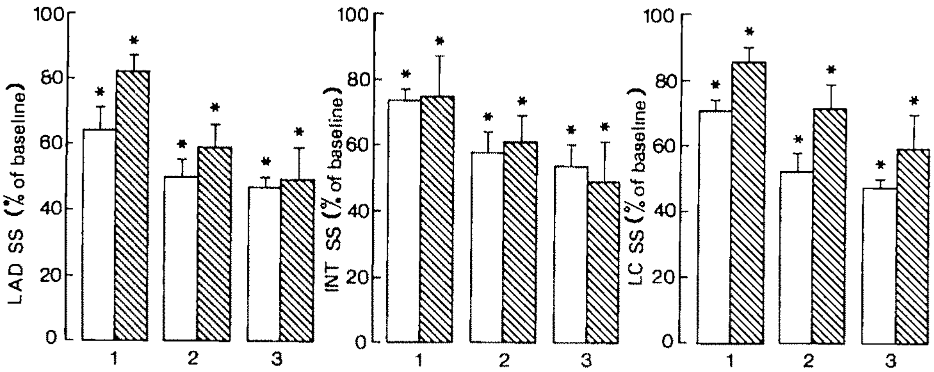

FIG. 5. The effects of lignocaine (open columns) and bupivacaine (cross-hatched columns) on systolic shortening (SS) in the apical (LAD), mid-wall (INT), and basal (LC) regions of the left ventricle. Values are expressed as a percentage of baseline values. 1 = Lignocaine 50 mg, bupivacaine 12.5 mg; 2 = lignocaine 100 mg, bupivacaine 25 mg; 3 = lignocaine 200 mg, bupivacaine 50 mg. $*P < 0.05$ *v.* baseline by two-way analysis of variance and Duncan's test.

these differences were seen with all three doses. Normalized SS data were compared between the local anaesthetics in the myocardial territories measured. Similar depression of SS occurred in the LAD, INT, and LC segments with both local anaesthetics (fig. 5).

DISCUSSION

Myocardial depression is a feature of the i.v. administration of lignocaine [16]. Laboratory investigations in awake animals, however, have shown stimulation of the cardiovascular system [17], which has been attributed to the central nervous system effects of lignocaine [8]. Bupivacaine, as well as other amide and ester local anaesthetics, is also a myocardial depressant [1,5,8,16,18]. Some investigators have reported that the degree of cardiovascular depression is related to anaesthetic potency [8], while others have suggested that bupivacaine is more cardiotoxic, especially in pregnancy and in situations of hypoxia and acidosis [6,19–21]. Many of the comparisons between lignocaine and bupivacaine have centred on the electrophysiological properties of the drugs. It now seems established that bupivacaine has a much greater, although somewhat unpredictable, potential to cause serious cardiac arrhythmias [5–7].

In the light of these apparent differences between lignocaine and bupivacaine on myocardial function, we have investigated their properties on global haemodynamics and regional wall motion in halothane-anaesthetized dogs. This general anaesthetic eliminated the potential influence of sympathetic nervous system activation caused by local anaesthetics [17]. We chose to give a bolus of a fixed dose of local anaesthetic, rather than on a dose per kilogram basis, to mimic accidental i.v. injection into the systemic circulation during the performance of regional anaesthesia, which is commonly administered as an empirical maximum dose rather than on a milligram per kilogram basis [22]. The first two doses of both lignocaine and bupivacaine would be comparable to those used for extradural and i.v. regional anaesthesia [1]. The ranges of blood concentrations at the time they were measured encompass those that would be expected after normal regional anaesthetic procedures. Thus, although undoubtedly within the toxic range after the bolus injections, the concentrations had returned to acceptable values well before the next injection was made [15]. The significant depression of LV dP/dt_{max} and of regional function in all myocardial segments seen with the initial and subsequent doses of the local anaesthetics agrees with previous reports of myocardial depression with these agents [1,5,8,16]. The depression of global haemodynamics (fig. 4) and regional myocardial function (fig. 5) was similar with lignocaine and bupivacaine.

It has been reported that PSS occurs in myocardium with compromised blood flow as the halothane concentration is increased [23]. PSS has also recently been observed in normal myocardium with normal coronary blood supply when verapamil was administered i.v. in combination with halothane [10,11]. As lignocaine and bupivacaine are sodium channel blockers, and may disturb calcium conductance, we performed the present study to determine if there was an interaction between these local anaesthetics and halothane producing regional dysfunction. PSS in the LAD region increased after the initial dose of bupivacaine and lignocaine, and this increase became significant after the second and third doses. Bupivacaine caused a significant increase in PSS after the initial dose in the INT region, but did not affect the LC region. Lignocaine caused an insignificant increase in PSS after each dose in the INT region, and significant regional dysfunction was present only after the second dose in the LC region. Thus regional dysfunction does occur with both lignocaine and bupivacaine, yet bupivacaine causes changes in the apex and mid-wall regions of the left ventricle, while lignocaine seems to cause predominantly apical dysfunction.

Bupivacaine differed from lignocaine in respect of effects on PR interval. There was a significant increase in PR interval after the second dose of bupivacaine, whereas lignocaine significantly slowed atrioventricular conduction only at the highest dose. This agrees with previous work suggesting that bupivacaine has a greater effect on myocardial conduction than lignocaine [5].

Lignocaine caused a reduction in CBF which was closely related to the reduction in CPP (fig. 1). Bupivacaine, however, had erratic effects on CBF when compared with those on CPP (fig. 3). This suggests differing effects on coronary conductance by these two agents. Both lignocaine and bupivacaine have been shown to be arteriolar constrictors in moderate doses [24,25], but the results of this study imply different properties with respect to the intact coronary vasculature. The effects of bupivacaine on CBF showed a wide scatter and suggest that, even with high CPP values, CBF is changed unpredictably and may be decreased precipitously.

The absolute values for PSS did not correlate with changes in CBF with either local anaesthetic (fig. 2). This suggests that the changes seen in PSS may result from an interaction between the local anaesthetics and myocardial cellular function rather than from alterations in regional blood supply, although redistribution of local blood flow and myocardial metabolic function were not examined. This may be related to the calcium channel blocking properties of these local anaesthetics, as an enhancement of the cardiodepressant effects of bupivacaine has been shown with nifedipine [26] and verapamil [27]. PSS may be a measure of altered contractile performance, possibly as a result of changes in myocardial membrane ion conductance, myocardial metabolism, or local subendocardial blood flow, induced by lignocaine and bupivacaine.

In summary, the i.v. administration of lignocaine or bupivacaine caused similar depression of global haemodynamics and regional myocardial function and the appearance of regional left ventricular asynchronous wall function (PSS). There was no relationship between PSS and CBF for either drug, and both drugs caused similar degrees of regional dysfunction, suggesting that regional contractile abnormalities are not the cause of the apparently increased cardiotoxicity of bupivacaine compared with lignocaine. The erratic effect of bupivacaine on CBF may result from changes in coronary vascular resistance; lignocaine, by comparison, exhibited more predictable CBF responses to i.v. injections.

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INHALATION ANAESTHETICS EXHIBIT PATHWAY-SPECIFIC AND DIFFERENTIAL ACTIONS ON HIPPOCAMPAL SYNAPTIC RESPONSES *IN VITRO*

M. B. MACIVER AND S. H. ROTH

SUMMARY

The effects of halothane, isoflurane and enflurane were compared on three CNS excitatory synaptic pathways in vitro, *to determine whether selective actions described* in vivo *result from differential effects on anatomically distinct cortical pathways and neurone populations. Halothane (0.25–1.25 vol%) depressed postsynaptic excitability of CA1 pyramidal neurones in response to activation of stratum radiatum synaptic inputs, and concentration-dependent excitatory (0.25–1.25 vol%) and depressant (1.5–2.0 vol%) actions were observed on dentate granule neurone excitability and perforant path evoked synaptic responses. In contrast, isoflurane increased CA1 neurone excitability (0.25–0.75 vol%) and produced postsynaptic depression of dentate neurones (0.5–4.0 vol%). Enflurane also increased CA1 excitability (0.5–4.0 vol%), but depressed synaptic responses at equivalent concentrations, and produced mixed excitatory (0.25–1.0 vol%) and depressant (1.0–4.0 vol%) effects on dentate synaptic responses. Differential actions were also observed for the three anaesthetics on stratum oriens excitatory inputs to CA1 neurones, and on antidromic responses. A good correlation (r = 0.992) exists between the membrane/buffer partition coefficients of these anaesthetics and their half-maximal concentrations for depression of synaptic responses; however, this correlation does not reflect the different, anaesthetic-specific actions observed. The results indicate that inhalation anaesthetics act at multiple and selective hydrophobic recognition sites which are heterogenously distributed on different synaptic pathways.*

General anaesthetics can depress synaptic transmission and neuronal excitability in the central nervous system (CNS) [1,2]. Although it is possible that CNS depression is the major action underlying anaesthesia, evidence exists for anaesthetic-induced facilitation of excitatory transmission [3–5] and various patterns of "activated" EEG recordings have been observed during anaesthesia [6,7]. Furthermore, anaesthetics produce agent-specific effects on CNS electrical activity *in vivo* [8], and a single anaesthetic state, or common neurophysiological mechanism, has not been observed for all anaesthetics. Concentration-dependent and anaesthetic-specific differential effects have also been reported on a number of invertebrate and isolated mammalian peripheral nervous system preparations [9]. These differential actions do not support a traditional "unitary" theory of anaesthesia [2,8–11]; rather, actions at multiple and selective membrane sites appear likely [12–14].

Recent studies of anaesthetic actions on vertebrate CNS neurones *in vitro* have not revealed differences in action between agents. For example, it was reported that a number of general anaesthetics (including inhalation agents and barbiturates) hyperpolarize neurones of the spinal cord and hippocampus [1], and a good correlation

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existed between concentrations required to produce hyperpolarization and those needed for anaesthesia. These authors suggested that membrane hyperpolarization produces a depression of CNS excitability which results in anaesthesia, and that *all* general anaesthetics share this common mechanism of action [15–17]. Halothane, isoflurane and enflurane, however, have been shown to *depolarize* hippocampal neurones [18], and the major common action of these anaesthetics appears to be depression of spontaneous discharge, via actions on spike initiation. The controversy concerning common *v.* differential actions of general anaesthetics prompted us to re-investigate the effects of inhalation agents on synaptic responses of mammalian CNS neurones *in vitro*.

METHODS

Preparation

Experiments were conducted on 73 hippocampal slices prepared from male Sprague–Dawley rats, as previously described [19]. A single slice from each rat was used and only one anaesthetic was studied on each preparation. Rats were anaesthetized with ether, the heart stopped by a blow to the back of the thorax and the brain rapidly removed and placed in pre-cooled (8–10 °C) oxygenated artificial cerebrospinal fluid (ACSF; see Materials). Transverse slices (400 µm) of hippocampus were cut using a vibratome (Campden Instruments, U.K.), following dissection of the dentate–hippocampal formation. The angles used to prepare slices for studies of CA1 and dentate granule (DG) pathways were approximately 5–10° on either side of the striation pattern of alveus fibres, to follow the lamellar organization of synaptic pathways in the rat hippocampal formation (fig. 1). Slices were placed on a nylon mesh screen at the gas/liquid interface in a Plexiglass tissue chamber. Oxygenated (95% oxygen–5% carbon dioxide and prewarmed (35 °C) ACSF was continuously perfused through the chamber at a rate of 1–1.5 ml min^{-1}. Slices were incubated for 1 h without electrical stimulation, followed by a 1–2 h period of control stimulation/recording to establish the stability of each preparation. All preparations used in this study exhibited field potential amplitudes of at least 5 mV (peak to peak) and control amplitude variability less than 5% during the initial data acquisition period, and following washout of anaesthetic.

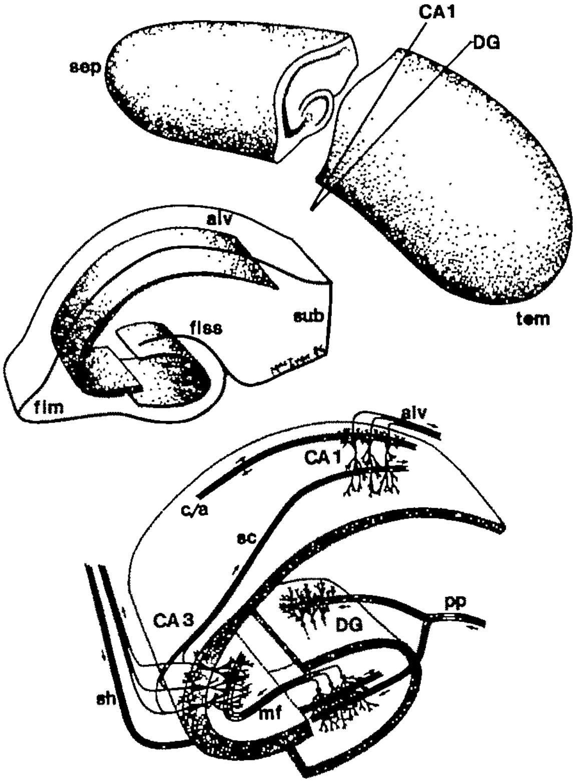

FIG. 1. Diagram of the rat hippocampal formation showing the angle used to prepare slices for CA1 pyramidal and dentate granule (DG) synaptic pathways. Stimulating electrodes were placed in stratum oriens to activate commissural/associational (c/a), or stratum radiatum to activate Schaffer-collateral (sc) inputs to CA1 pyramidal neurones. Dentate granule evoked field potentials were produced by stimulating perforant path (PP) fibres. Antidromic responses were produced by stimulating the alveus (alv) or mossy fibre (mf) pathways, for CA1 or DG responses, respectively. sep = Septal; tem = temporal; fim = fimbria; fiss = hippocampal fissure; sub = subiculum; sh = septo-hippocampal fibres.

Electrode placement

Bipolar nichrome stimulating electrodes were placed on perforant path fibres, stratum radiatum, or stratum oriens to activate excitatory synaptic inputs to DG or CA1 pyramidal neurones, respectively (fig. 1). Antidromic responses were produced by stimulation of the alveus or mossy-fibre pathways. Extracellular glass recording electrodes (sodium chloride 2 mol $litre^{-1}$, 2–10 MΩ) were placed in the cell body regions of DG and CA1 areas to record stimulus-evoked field potentials. Paired stimulus pulses of 0.01–0.05 ms duration (10–80 µA) were delivered at 0.1 Hz.

Stimulus intensity was varied to determine input/output relationships (E–S analysis) at a fixed interstimulus interval of 18–25 ms [20–22]. Recorded signals were amplified (× 1000), filtered (1 Hz to 10 KHz, bandpass), and digitally stored for later analysis (40 μs resolution on a PDP 11/23 UNIX system). Population spike (PS) amplitudes were measured from threshold to peak negativity and excitatory post-synaptic potential (EPSP) rise times (dV/dt) were determined from the initial EPSP slope by linear regression analysis of digital sample points between 20 and 80 % of the EPSP peak positivity [19]. All records shown are single sweeps of 2048 sample points.

Administration and analysis of anaesthetics

The inhalation agents were applied as vapours to the tissue chamber via the pre-warmed and humidified oxygen–carbon dioxide gas stream above the slices, using calibrated commercial vaporizers. Concentrations, expressed as volume percent (vol %), refer to settings on the vaporizer dials. To reach equilibrium, vapour concentrations were applied for a minimum of 30 min. The onset times for drug effects were often less than 1 min, and maximum effects reached a plateau within 15 min. Accurate measurements of concentrations in the perfusate were made using a Hewlett-Packard 5880A gas chromatograph fitted with a glass column (packed with Poropak Q) and flame ionization detector. The carrier gas was nitrogen delivered at a flow rate of approximately 40 ml min^{-1}. Temperatures of the injector, oven and detector were 155, 140 and 170 °C, respectively. Aqueous test samples (20 μl) were taken from the recording chamber with a gas-tight Hamilton syringe and injected directly onto the column. Peak area values from the test samples were plotted against those of known concentrations of standards, to determine bath concentrations. Values were determined as peak area ratios relative to dextrose, which was used as an internal standard in the ACSF. Column retention times were approximately 3–5 min for the inhalation anaesthetics and 7.5 min for dextrose.

Materials

Adult male Sprague–Dawley rats (150–250 g) were obtained from the University of Calgary Biosciences Vivarium. Anaesthetics were obtained from the following suppliers: halothane from Halocarbon (Ontario) Ltd (Mississauga, Ont.), enflurane and isoflurane from Ohio Medical Anaesthetics (Pointe Claire, Que.). The vaporizers were manufactured by Ohio Medical Products (Madison, Wis.). The ACSF physiological solution [23] had the following composition (mmol litre^{-1}): NaCl 134, KCl 4.5, $CaCl_2$ 1.6, KH_2PO_3 1.25, $MgSO_4$ 2, $NaHCO_3$ 16, dextrose 10; modified by adjusting calcium and potassium concentrations to values measured *in vivo* [24].

RESULTS

Field potential responses

Typical field potential recordings from the three synaptic pathways are shown in figure 2. Stratum radiatum (RAD) to CA1 evoked responses exhibited the largest PS amplitudes, with interstimulus intervals of 22–25 ms producing maximal paired pulse potentiation. Stratum oriens (OR) to CA1 evoked responses were smaller in amplitude and an interpulse interval of 20–22 ms was optimal for paired pulse potentiation. Stimulation of perforant path (PP) inputs to dentate granule neurones produced the largest EPSP amplitudes, although PS amplitudes were usually smaller than CA1 responses. Dentate EPSP responses had faster rise times and a shorter half-time for decay, compared with CA1 responses, and interstimulus intervals of 16–20 ms produced maximal paired pulse potentiation.

Halothane. Low concentrations of halothane (0.3–1.25 vol %) produced depression of PS responses for RAD inputs to CA1 neurones (upper recordings in figure 2A). PS depression occurred with little or no effect on field EPSP amplitudes (compare responses to the first *v.* second stimuli). Depression of PS responses did not appear to result from altered paired pulse potentiation, since facilitation of EPSP responses was not altered. The latency to onset and initial slope of the EPSP was not changed in the presence of halothane concentrations less than 1.5 vol %; however, higher concentrations depressed EPSP responses and complete block of transmission occurred at 3.0 vol %, at all stimulus intensities (see below (E–S relationships)).

EPSP responses evoked by OR inputs to CA1 were depressed by the lowest effective concentrations of halothane (0.25–1.25 vol %; middle recordings of figure 2A). Depression of EPSP responses was accompanied by reduced PS amplitudes. Onset latency and paired pulse potentiation of the EPSP were not altered by

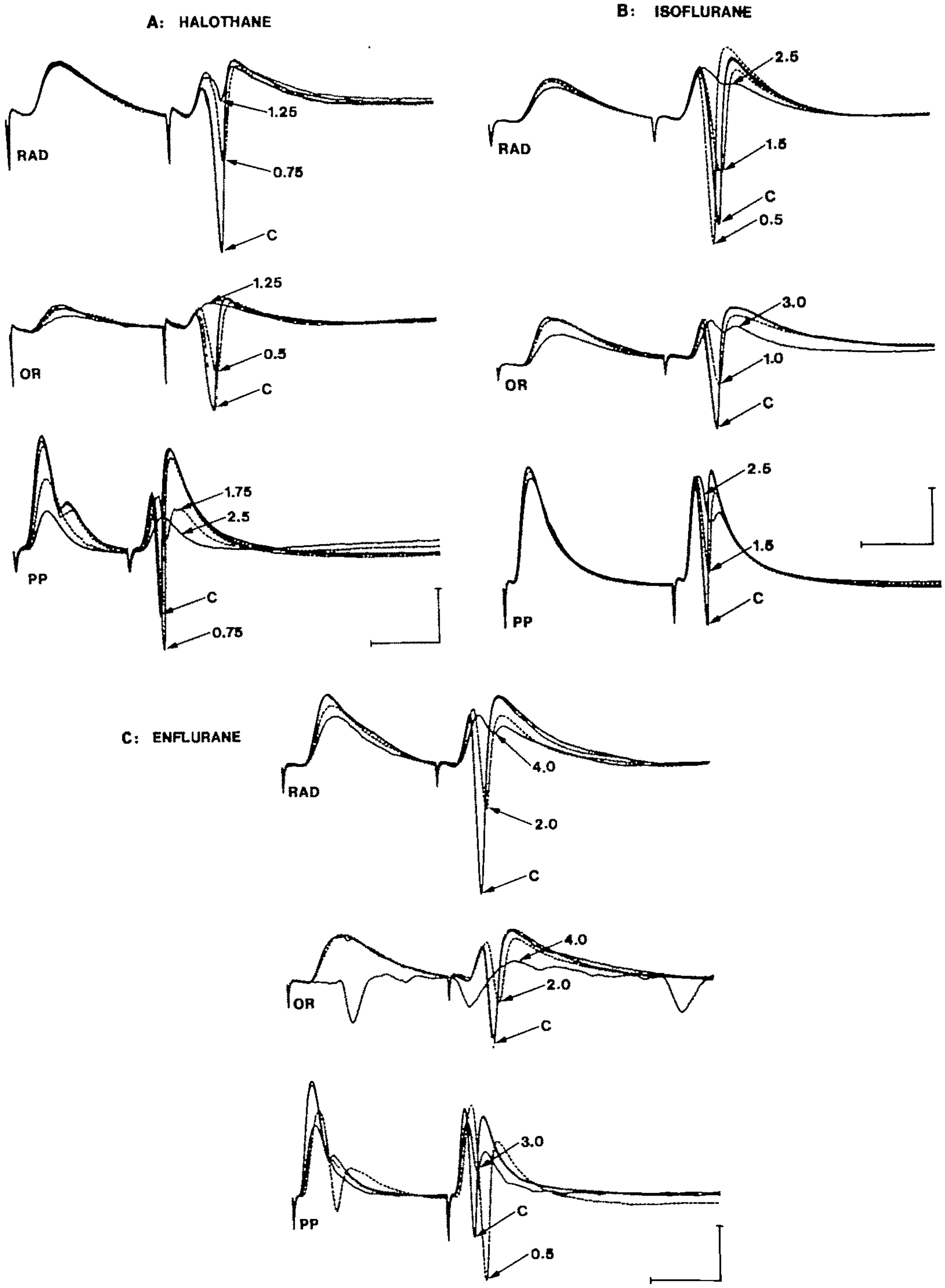

FIG. 2. A: Effects produced by halothane on stratum radiatum (RAD), stratum oriens (OR) inputs to CA1 neurones, and perforant path (PP) inputs to dentate granule neurone evoked field potentials. Each superimposed series of records shows control (C) responses before (solid line) and after washout (light dotted line) together with two or three concentrations of anaesthetic (numbers refer to vol %). B: Effects produced by isoflurane on evoked field potentials. C: Effects of enflurane on evoked responses. Calibration: 20 ms and 2.0 mV for A, B and C. Data in each series of records are from separate preparations.

concentrations which completely blocked PS responses (1.0–1.5 vol %).

The lower recordings in figure 2A illustrate the different profile of effects produced by halothane on PP inputs to dentate granule neurones, compared with the CA1 responses described above. Low concentrations (0.5–1.25 vol %) increased PS amplitudes, whereas EPSP responses were either unchanged or slightly depressed. Latencies for onset of both the EPSP and PS were increased at concentrations which enhanced PS amplitudes. Concentrations of halothane greater than 1.5 vol % depressed both EPSP and PS responses. Paired pulse facilitation of the EPSP was not observed at concentrations greater than 2.0 vol % (compare responses to the first v. second stimuli at 2.5 vol % in figure 2A).

Isoflurane. The effects produced by isoflurane differed from the actions of halothane on both the RAD and PP synaptic pathways (compare figure 2A with 2B). Low concentrations of isoflurane (0.25–0.9 vol %) increased RAD to CA1 PS amplitudes, whereas EPSP responses were unchanged or slightly depressed (upper recordings in figure 2B). Increased PS amplitudes were accompanied by decreased latencies of the spike; but onset latencies, rise time of the EPSP, and paired pulse potentiation were not consistently altered at these concentrations. Concentrations greater than 1.0 vol % produced depression of PS responses, accompanied by increased latencies and broadening of the negative spike (e.g. 1.5 vol % in figure 2B). Concentrations greater than 2.0 vol % depressed synaptic (EPSP) responses and above 3.0 vol % completely blocked postsynaptic discharge, although paired pulse facilitation of EPSP was still apparent.

In contrast to the biphasic actions on RAD inputs, isoflurane produced only depression of OR inputs to the same postsynaptic population (CA1). Concentrations from 0.5 to 4.0 vol % depressed both EPSP and PS responses, and this was accompanied by increased latencies (middle recordings in figure 2B). Paired pulse potentiation was observed at concentrations up to 4.0 vol % for this pathway.

The actions of isoflurane on PP inputs to DG neurones are shown in the lower recordings of figure 2B. All effective concentrations depressed PS responses, with only minimal effects on the EPSP. Even in the presence of concentrations which markedly depressed PS amplitudes (e.g. 2.5 vol %), EPSP amplitudes, rise times and onset latencies were only slightly altered (compare EPSP and PS responses to the first and second stimuli, respectively). Concentrations greater than 3.0 vol % were required to depress EPSP responses in this pathway; this is well above the values needed to alter EPSP amplitudes for either of the inputs to CA1 neurones.

Enflurane. Alterations in field potential produced by enflurane are illustrated in figure 2C, and marked differences in effect were observed compared with halothane and isoflurane. RAD inputs to CA1 neurones were depressed by enflurane over the concentration range 0.5–4.0 vol % (upper recordings in figure 2C). EPSP responses were depressed at the lowest concentrations, and reduced PS amplitudes appeared to result from depression of synaptic input (see below (E–S relationships)). Paired pulse potentiation and onset latencies for EPSP were not markedly altered by concentrations less than 4.0 vol %, but an increased latency for PS responses accompanied depression of spike amplitudes.

Low concentrations of enflurane (below 2.5 vol %) did not alter EPSP responses for OR inputs to CA1 (middle recordings of figure 2C). PS amplitudes were depressed by concentrations as low as 0.5 vol % and complete depression occurred above 4.0 vol %. Concentrations greater than 2.0 vol % produced intermittent burst discharges from CA1 neurones, as previously described [19]. This seizure-like activity occurred both spontaneously and in response to stimulation of RAD and OR inputs to CA1 neurones (e.g. at 4.0 vol % in middle recordings of figure 2C). Burst firing, however, did not occur in response to each stimulus, and non-burst responses were chosen for the other records shown in figure 2C, for comparison with the non-burst responses in the presence of halothane and isoflurane.

Enflurane produced concentration-dependent biphasic actions on PP inputs to DG neurones (lower recordings in figure 2C), similar to the effects produced by halothane. Concentrations from 0.25 to 1.0 vol % produced increased PS amplitudes accompanied by prolonged spike latencies (e.g. at 0.5 vol % in figure 2C) and increased EPSP onset latencies. Note that the EPSP amplitude and rise time were depressed by concentrations which increased PS responses. Higher concentrations of enflurane (1.0–6.0 vol %) produced further reduction in EPSP

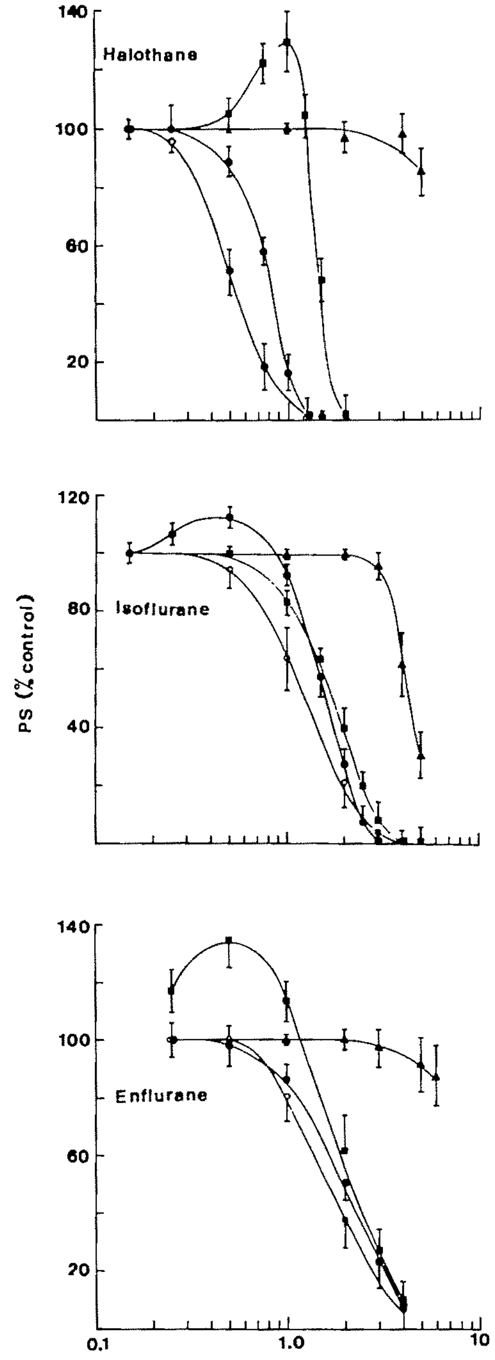

FIG. 3. Concentration-response curves for halothane, isoflurane and enflurane actions on stratum oriens (○), stratum radiatum (●), perforant path (■) and CA1 antidromic (▲) responses. Population spike (PS) amplitudes are expressed as percent of control for various concentrations (vol%) of anaesthetic; each point is the mean ± SEM from 3 to 7 experiments; effects were measured at equilibrium.

responses, resulting in depression of PS amplitudes. Paired pulse potentiation was not altered by concentrations less than 4.0 vol%.

Concentration–response relationships

Concentration–response curves were different for each of the three volatile anaesthetics on the synaptic pathways studied (fig. 3). Note the dissimilar biphasic effects (enhancement/depression) *v.* monophasic responses on different pathways. Facilitation of PS responses were observed at the lowest effective concentrations for all three anaesthetics on one of three pathways for each agent. The major common effect on all pathways was depression of PS amplitudes in the presence of higher concentrations; halothane was most potent, producing half-maximal (ED_{50}) depression of PS amplitudes at 0.5, 0.8 and 1.5 vol% for oriens, radiatum and perforant path inputs, respectively; isoflurane produced half-maximal depression at 1.25, 1.6 and 1.8 vol% and enflurane was the least potent, with ED_{50} values of 1.65, 2.0 and 2.15 vol%. The ED_{50} values for depression of stratum radiatum inputs to CA1 neurones corresponded to perfusate concentrations of 0.4, 0.6, and 0.9 mmol litre^{-1} for halothane, isoflurane and enflurane, respectively, measured using gas chromatographic analysis (see Methods). Depression of CA1 antidromic responses required 5 to 10 times greater concentrations for minimal effects. Half-maximal depression of antidromic PS amplitudes could not be achieved with halothane and enflurane, limited by the maximum range of the vaporizers (fig. 3). Similar effects were produced by these agents on antidromic responses of dentate granule neurones (data not shown), except in the presence of enflurane (0.5–3.0 vol%), which increased dentate antidromic PS amplitudes [19].

E–S relationships

The relationship between the rise times (dV/dt) of the positive synaptic potential (EPSP) and the amplitude of the negative population spike (PS) describes an input/output function for a synaptic pathway [20,21,25]. The intercept on the EPSP axis provides a measure of postsynaptic discharge threshold [22,23,26]. To determine whether the inhalation anaesthetics altered postsynaptic excitability to a greater extent than synaptic function, E–S relationships for stratum radiatum and perforant path responses were studied.

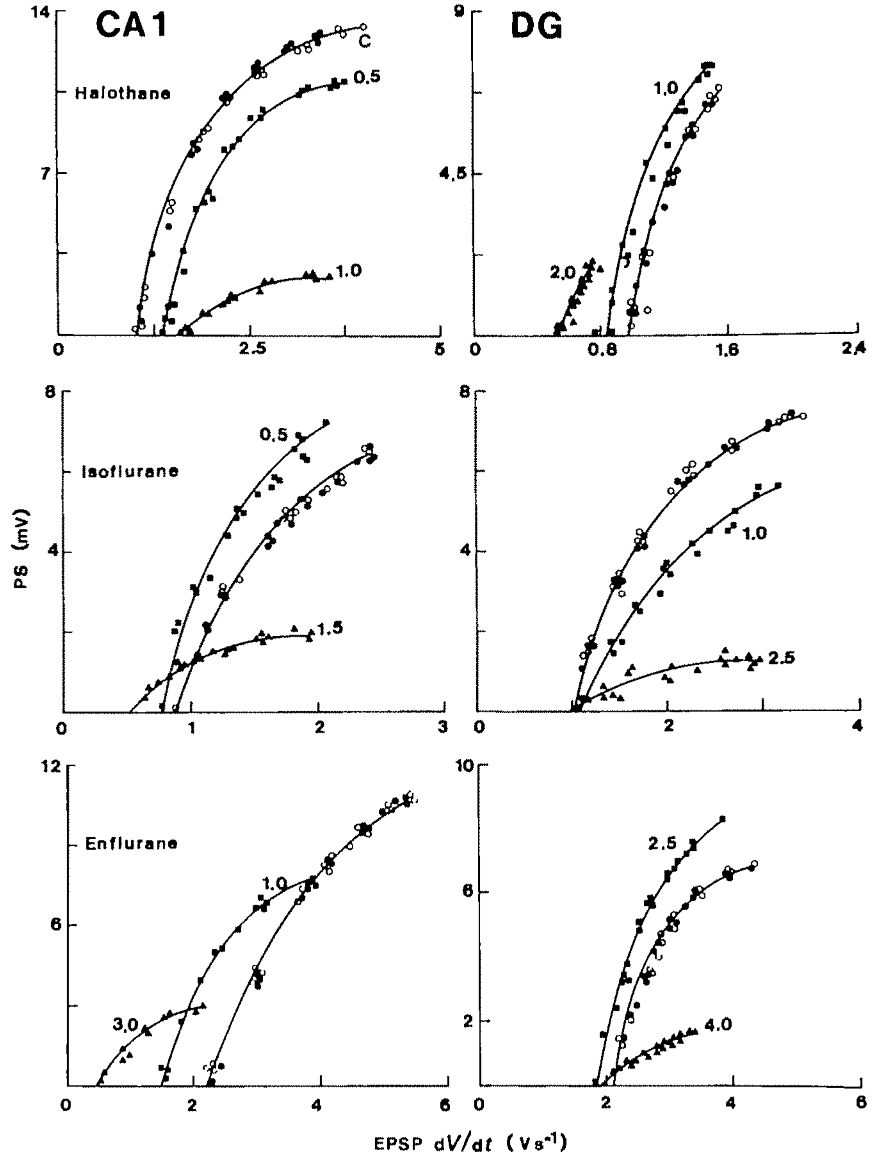

FIG. 4. E–S curves for stratum radiatum inputs to CA1 pyramidal neurones and perforant path inputs to dentate granule (DG) neurones in the presence of various concentrations (vol %) of halothane, isoflurane and enflurane. Control (C) responses are also shown: pre-anaesthetic (○) and post-recovery (●). Data for each graph are from separate preparations.

As shown in figure 4, a steep relationship between the EPSP and PS was apparent at low stimulus intensities, and PS responses approached a maximum at the higher intensities [20, 22]. Data in each graph are from separate preparations. Each point represents the EPSP rise time and amplitude of the associated PS, measured at the second single stimulus intensity, from a trial of 24 test stimuli at eight to 10 different intensities. If a stimulus failed to elicit a PS response or if burst discharges were produced (i.e. in the presence of enflurane), the point was not plotted.

Halothane. Population spike responses for RAD inputs to CA1 appeared to be most sensitive to the depressant effects of halothane (upper left, figure 4). Stimuli which produced equivalent EPSP responses failed to elicit PS amplitudes comparable to control values, indicating that depression of postsynaptic excitability was the major action on this pathway. Depression of excitability was also apparent from the shift to the right of the EPSP axis intercept (threshold), such that larger EPSP responses were required to produce minimal discharge of the CA1 population.

In the upper right of figure 4, the effects of halothane on PP inputs to dentate granule neurones are shown. Low concentrations (e.g. 0.5 vol %) produced a shift to the left in the EPSP axis intercept and increased PS amplitudes were observed for comparable control EPSP responses, indicating that a decreased threshold for discharge of granule neurones could account for the enhancement of field potentials at concentrations of 0.25–1.25 vol %. In the presence of higher concentrations (e.g. 1.5 vol %), depression of synaptic input resulted in decreased PS amplitudes, even though discharge threshold was further reduced.

Isoflurane. Isoflurane produced opposite effects, compared with halothane, on E–S profiles for RAD and PP pathways (fig. 4). Low concentrations (e.g. 0.5 vol %) enhanced PS amplitudes for equivalent control EPSP responses and also appeared to decrease the discharge threshold of the CA1 population. Higher concentrations (e.g. 2.0 vol %) produced a further reduction of discharge threshold; however, at higher stimulus intensities, PS amplitudes were reduced. Isoflurane produced two opposing effects on CA1 postsynaptic excitability: enhanced excitability, such that smaller EPSP dV/dt responses could discharge the CA1 population, and depression of the level of discharge at stimuli above threshold.

The major action of isoflurane on PP inputs to dentate neurones was a depression of PS amplitudes (middle right of figure 4). Even in the presence of high concentrations (e.g. 2.5 vol %) EPSP responses were only slightly depressed (10 %), while PS amplitudes were reduced by approximately 80 % of control. This is opposite to the effects of halothane, which depressed EPSP responses but enhanced the excitability of dentate neurones. Isoflurane did not alter the EPSP axis intercept, suggesting that the depression of granule neurone discharge did not result from an increase in PS threshold.

Enflurane. All effective concentrations of enflurane produced a dramatic reduction of discharge threshold for CA1 neurones (lower left of figure 4), which may account for the spontaneous and stimulus-evoked seizure-like burst firing previously described for this anesthetic [5, 19]. The dominant effect on RAD inputs to CA1, however, was depression of synaptic responses (EPSP), resulting in an overall attentuation of field potential amplitudes. Enflurane appeared to act on at least two independent sites, depressing synpatic transmission and enhancing CA1 neurone excitability.

PP to dentate neurone EPSP responses were also depressed by enflurane (lower right of figure 4), but the major effect occurred on postsynaptic excitability. In the presence of low concentrations (e.g. 0.25 vol %) depressed synaptic responses were accompanied by increased PS amplitudes, which appeared to involve a reduction in discharge threshold (left shift of the EPSP axis intercept). Higher concentrations (e.g. 3.0 vol %) produced a further reduction of EPSP responses and marked depression of PS amplitudes. Enflurane did not produce dramatic reductions in discharge threshold of granule neurones, and burst firing of dentate cells was not observed [19].

DISCUSSION

Halothane, isoflurane and enflurane were capable of depressing field potential responses in the three synaptic pathways studied; however, the concentration-dependent effects were different for each anaesthetic. This is apparent when comparing the biphasic (facilitation/depression) *v.* monophasic actions on population spike amplitudes (fig. 3). Furthermore, depression of field potential amplitudes could result from opposing actions on synaptic responses (EPSP) and postsynaptic excitability (PS) of CA1 pyramidal and dentate granule neurones (fig. 4). These varied and opposing effects suggest that inhalation anaesthetics act via different mechanisms at selective cellular (membrane) sites. We propose that inhalation anaesthetics interact with discrete membrane "recognition" sites which can discriminate between agents on the basis of molecular structure. Landau and colleagues [27] have demonstrated that ether and methoxyflurane can produce biphasic actions on miniature end-plate currents at the frog neuromuscular junction. They concluded in their report that "the effect of such structurally non-specific drugs comprises a combination of discrete and distinguishable events which are specific and dose dependent for each of the agents". The results of the present study complement their observations and extend the hypothesis to mammalian nervous tissue.

Pathway-specific actions of inhalation anaesthetics

In addition to the obvious morphological differences between CA1 pyramidal neurones and dentate granule cells, there are also several important differences in membrane physiology [28]. Granule cells exhibit a relatively high resistance to convulsant-induced burst firing, which has been attributed to a lack of inward calcium currents [29]. CA1 pyramidal neurones, in contrast, exhibit a low threshold for convulsant-induced seizure activity, and large inward calcium currents have been recorded [30]. Therefore, distribution of membrane calcium channels may differ between the two populations. Given that glutamate is a likely transmitter in both PP and RAD circuitry, the differential actions of anaesthetics could also be accounted for by the differences in distribution of glutamate receptor sub-types in CA1 and DG regions [31].

In the present study, marked differences in anaesthetic effects on synaptic responses and postsynaptic excitability were observed between the different pathways and neurone populations. Halothane blocked transmission in the stratum radiatum by depressing CA1 neurone excitability, but perforant path inputs to dentate granule neurones were blocked via a reduction in synaptic strength sufficient to overcome a halothane-induced increase in granule neurone excitability (fig. 4). Enflurane enhanced the discharge of CA1 neurones, but depressed the stratum radiatum-evoked EPSP. In contrast, the major effect of enflurane on dentate granule neurones was a depression of discharge. EPSP responses for radiatum and oriens inputs to CA1 neurones were more sensitive to isoflurane than EPSP responses for perforant path inputs to dentate neurones (fig. 2B), yet depression of discharge was observed on both populations of neurones (fig. 4).

It is possible that anaesthetic recognition sites are differentially distributed on the same population of neurones. Isoflurane, for example, enhanced the discharge of CA1 neurones by reducing threshold (fig. 4), and this resulted in larger population spike amplitudes following stimulation of RAD inputs. This reduction in threshold for CA1 discharge in response to RAD stimulation was not generalized to OR inputs, since only a depression of stratum oriens-evoked population spikes was observed (fig. 2B). Enflurane also reduced the discharge threshold of CA1 neurones when RAD inputs were tested, but an increase in OR-evoked population spikes was not observed, even though EPSP amplitudes were not depressed and spontaneous burst discharges were generated by the CA1 neurone population. These anaesthetics produced different effects on the postsynaptic discharge of CA1 neurones, dependent on which synaptic input brought the population to threshold. A differential distribution of anaesthetic sites in basilar and apical dendrites of CA1 neurones could account for the different effects on postsynaptic excitability.

Concentration-dependent biphasic responses

Anaesthetics produce unique patterns of excitatory and depressant effects *in vivo*, and specific brain regions are differentially affected by the same anaesthetic [5, 8]. Similar patterns of concentration-dependent biphasic actions have also been reported for anaesthetics on relatively simple invertebrate neuronal preparations [9, 32–34].

Previous studies of general anaesthetic effects on isolated mammalian CNS preparations have not described biphasic excitatory and depressant actions. Depression of excitatory synaptic responses [2], enhancement of synaptic inhibition [35, 36], or decreased postsynaptic excitability [3, 37] were the dominant actions reported for isolated mammalian neurones. Recent studies using the rat hippocampal slice preparation [1, 15] suggest an enhanced potassium conductance as the major common action leading to depression of CNS excitability [17], and direct depression of CA1 discharge (that is, via sodium channel blockade) also appears to be an important action for the inhalation anaesthetics [18]. However, a single common effect (e.g. enhanced potassium conductance) or "unitary" mechanism, *per se*, cannot account for the selective and pathway-specific effects observed in the present study.

A summary of the differential effects on radiatum, oriens and perforant path field potential responses is provided in table I, together with a comparison of the actions of barbiturates on the three synaptic pathways [38]. The only agent which produced a common action on all three pathways and two neurone populations was phenobarbitone—as indicated by a "universal"

TABLE I. *Differential effects of anaesthetics on hippocampal synaptic transmission. RAD = Stratum radiatum inputs to CA1; OR = stratum oriens inputs to CA1 pyramidal neurones; PP = perforant path inputs to dentate granule (DG) neurones. Anti. = Antidromic field potential amplitude; Excit. = excitability from the EPSP axis intercept of Input/Output curves—increased excitability means a smaller EPSP dV/dt was able to produce discharge of the postsynaptic neurones. Black arrows = major effect; open arrows = minor effect; direction of arrow = an increase (up) or decrease (down) in response relative to pre-anaesthetic control responses. Concentration-dependent biphasic effects are indicated (↑↓), with the arrow on the left for the lowest effective concentration. — = Lack of effect*

	Effect on field potential responses									
	RAD		OR		PP		CA1		DG	
Anaesthetic	EPSP	PS	EPSP	PS	EPSP	PS	Anti.	Excit.	Anti.	Excit.
Pentobarbitone [38]	↑↓	↑↓	↓	↓	↑↓	↓	↓	↓	↓	—
Phenobarbitone [38]	↓	↓	↓	↓	↓	↓	↓	↓	↓	—
Halothane	↓	↓	↓	↓	↓	↑↓	↓	↓	↓	↑
Isoflurane	↓	↑↓	↓	↓	↓	↓	↓	↑	↓	—
Enflurane	↓	↓	↓	↓	↓	↑↓	↓	↑	↑↓	—

depression of EPSP, PS and antidromic field potentials. Pentobarbitone, halothane, isoflurane and enflurane produced pathway-specific actions (compare biphasic and monophasic actions on EPSP and PS of RAD, OR and PP synaptic responses). The anaesthetics also altered the postsynaptic excitability of CA1 and DG neurone populations in a differential manner; for example, halothane increased the excitability of DG but depressed CA1 neurones (table I). The other agents studied did not alter DG neurone excitability, but produced variable effects on CA1 discharge threshold. As indicated above, the marked decrease in CA1 discharge threshold produced by enflurane may account for its seizure-inducing properties.

Several of the recorded responses (OR, EPSP and PS; CA1 antidromic) were "universally" depressed by all five anaesthetics (table I), although the degree of depression varied between agents; that is the major action of pentobarbitone on OR evoked responses was depression of PS amplitudes, in contrast to phenobarbitone which produced depression of synaptic input (EPSP) to a greater extent than CA1 discharge (PS). All other responses were differentially affected by the anaesthetics; for example pentobarbitone and isoflurane produced biphasic effects on RAD-evoked PS responses, phenobarbitone and halothane produced marked depression, and enflurane only marginally depressed this response (table I). The barbiturates and halothane depressed CA1 discharge, but enflurane and isoflurane increased the excitability of CA1 neurones (table I). Thus the anaesthetics studied exhibited some common actions, but also a number of distinctly different effects. The particular profile of effects observed was dependent on any combination of the anaesthetic, concentration, synaptic pathway, neurone population, and the response (EPSP or PS) measured.

Correlation between synaptic actions and anaesthetic potency

Major support for a "unitary" theory of anaesthetic action originates from the observed correlation between anaesthetic potencies and partition coefficients for membrane/buffer or solvent/water systems [39]. A correlation ($r = 0.992$) exists between Log membrane/buffer partition coefficients and Log ED_{50} concentrations required to depress stratum radiatum synaptic transmission in the present study. The correlation was not markedly changed by including data for pentobarbitone and phenobarbitone ($r = 0.983$) (fig. 5A), and depression of stratum radiatum transmission was better correlated with predicted *in vivo* potencies than were the minimum effective concentrations for producing hyperpolarization reported by Nicoll and Madison [1]. The correlation was improved ($r = 0.991$) by omitting data for phenobarbitone (fig. 5B), which is not an effective anaesthetic *in vivo* [35].

Membrane recognition sites and the mechanisms of action of anaesthetics

The results of the present study are best explained by anaesthetic interactions with hydrophobic microdomains in neuronal membranes, thus accounting for the correlation between

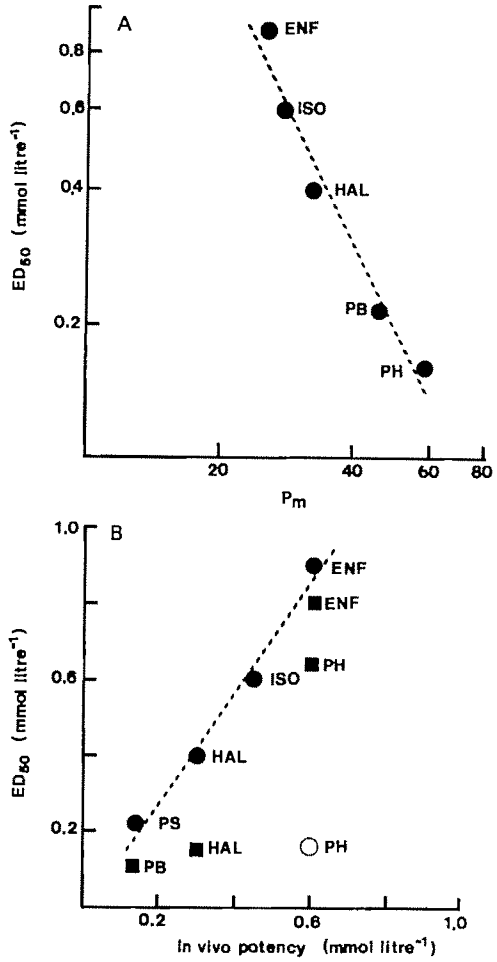

FIG. 5. Stratum radiatum to CA1 pyramidal neurone PS responses (ED_{50}) (mmol litre^{-1}) compared with: A membrane/buffer partition coefficients (P_m); B: *in vivo* anaesthetic potencies (circles) and with minimum effective concentrations for hyperpolarization of spinal cord neurones (■) (data from [1]). ENF = Enflurane; ISO = isoflurane; HAL = halothane; PB = pentobarbitone; PH = phenobarbitone.

potency and membrane/buffer partition coefficients. However, a high degree of selectivity has been demonstrated for anaesthetic recognition sites, as indicated by the different potencies for stereoisomers of pentobarbitone [32,38] and the differential (biphasic, monophasic, burst-inducing) effects of structural isomers such as enflurane and isoflurane.

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RAT LIVER SLICES AND DIAZEPAM METABOLISM: *IN VITRO* INTERACTIONS WITH VOLATILE ANAESTHETIC DRUGS AND ALBUMIN†

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Hepatic drug extraction is limited by the blood flow to the liver, by barriers between blood and the site of metabolism such as drug serum protein binding, and by the intrinsic clearance of the drug from the organ [1]. The last factor reflects the activity of the drug metabolizing enzymes. For restrictively eliminated drugs such as diazepam, the hepatic extraction is confined to the free fraction in serum and independent of liver blood flow. Consequently, hepatic elimination of diazepam depends on enzyme activity and serum protein binding [2]. It follows that any action taken to change either of the two factors would result in altered hepatic elimination of diazepam.

Volatile anaesthetic agents inhibit the hepatic metabolism of other drugs *in vitro* [3–5]. Volatile anaesthetics have been shown also to decrease drug metabolism *in vivo* in both animals and man [6–12]. Halothane seems to be a more potent inhibitor of drug metabolism than enflurane and isoflurane [8, 9].

Recent evidence suggests that the volatile anaesthetics or their metabolites interact with drug serum protein binding [13–17], the other factor of significance for hepatic elimination of diazepam. The presented *in vitro* data invite the conclusion that the binding of diazepam to albumin, its major binding protein, is especially sensitive to this effect of the agents. Furthermore, enflurane and the halothane metabolite trifluoroacetic acid proved to be the most potent displacers of diazepam.

SUMMARY

The influence of the volatile anaesthetic agents enflurane, isoflurane, halothane and the halothane metabolite trifluoroacetic acid was studied on the hepatic elimination of diazepam, by incubating precision-cut slices of rat liver in a closed system. The impact of anaesthetic-induced action on enzyme activity and diazepam binding to human serum albumin (HSA) was assessed in protein free and protein containing buffers, respectively. Human serum albumin reduced the elimination of diazepam by 12 and 50% at concentrations of 1 and 10 mg ml^{-1}, respectively. In the absence of albumin, halothane 1 mmol litre^{-1} reduced the elimination of diazepam by 13%, whereas enflurane at 1.5 mmol litre^{-1} caused a reduction of 8%. No effect was seen from isoflurane 1 mmol litre^{-1} and trifluoroacetic acid 4 mmol litre^{-1}. In the presence of the highest concentration of albumin, however, an increased elimination of diazepam of 24% resulted from exposure to enflurane and trifluoroacetic acid, while no statistically significant changes were seen for isoflurane and halothane. The present work supports the view that volatile anaesthetic agents may cause pharmacokinetic drug interactions by interference with both enzyme activity and drug protein binding.

New techniques for cutting and incubation of liver slices have been established [18, 19]. Slices, as opposed to isolated hepatocytes, maintain tissue integrity, and the incubation system described

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allows for the introduction of extrahepatic pharmacokinetic factors such as drug binding to serum proteins [20]. In this closed system the presence of the two above mentioned factors governing hepatic elimination of diazepam, and the interacting volatile agents, is secured.

Thus, the aim of the present study was to investigate the effect of volatile anaesthetic-induced inhibition of metabolizing enzymes and protein binding on hepatic elimination of diazepam. Incubation of rat liver slices in a closed system was used as an *in vitro* method for this purpose.

METHODS

Slice preparation and incubation

Non-induced male Sprague–Dawley rats (225–300 g) from Harlan were killed by decapitation. The livers were excised immediately and placed in ice-cold Krebs–Henseleit buffer (pH 7.40) under constant aeration (95% oxygen–5% carbon dioxide). Slices of approx. 15 mg were produced in a standardized manner according to the method of Krumdieck, dos Santos and Ho [18] using a modified device [19]. Two slices were placed on the inside wall of cylindrical stainless steel roller screens. These were inserted into 20-ml glass scintillation vials (Kimbel, Ohio) with 1.7 ml of Krebs–Ringer–Hepes buffer, gassed with 95% oxygen–5% carbon dioxide, capped with rubber caps and placed horizontally on a vial rotator at 2 rev min^{-1} at 37 ± 1 °C [19].

Drug interaction studies

Before the drug interaction studies, slices were preincubated for 30 min at 37 °C in Krebs–Ringer–Hepes buffer containing diazepam 2.5 µmol litre^{-1}. The concentration of diazepam used was in the upper clinical range [21], but should not have saturated the biotransformation enzymes [2]. Thereafter, the gently blotted roller screens were transferred to new sets of scintillation vials with fresh buffer containing 2.5 µmol litre^{-1} of diazepam only, or with 1 or 10 mg ml^{-1} of human serum albumin (HSA) in addition. These vials were also gassed with 95% oxygen–5% carbon dioxide and incubated for 2 h. A buffer pH of 6.95 resulted from this procedure. Blanks were incubated without slices and controls were incubated in the absence of any interacting agents. Exposed slices were incubated with halothane, enflurane, isoflurane or trifluoroacetic acid. The volatile anaesthetics were injected (2–10 µl) through rubber caps by a micro syringe (Hamilton) to achieve buffer concentrations ranging from 0.4 to 1.5 mmol litre^{-1}. Concentrations of 0.8 and 4 mmol litre^{-1} were used for the halothane metabolite, trifluoroacetic acid. The given concentrations were all in clinically relevant ranges [22–24]. The buffer solutions were stirred for at least 2 h before being pipetted into the scintillation vials. Four or five experiments (one animal for each) were performed for each of the interacting agents, with two vials for each group in any experiment. Tissue samples from one rat were thus exposed to all anaesthetic agents.

Analysis of diazepam

To 0.9 ml of the sample of buffer from the incubation vials was added 0.1 ml of the internal standard, prazepam 10 µmol litre^{-1}, and the mixture extracted into 1 ml of hexane:methanol (19:1). The residue from the top organic layer was reconstituted into the mobile phase (acetonitrile:water (1:1)) after agitation, centrifugation and evaporation. Analysis was performed on a Beckman 332 high performance liquid chromatograph equipped with a 50-µl loop and a C-18 reverse phase column, based upon u.v. detection at 229 nm, and recorded on a Hewlett-Packard 3380A integrator. Standard curves (0.1–5.0 µmol litre^{-1}) were linear through the origin. Coefficients of variation within day and day-to-day ($n = 5$) were both 2%.

Other analyses

Concentrations of volatile anaesthetics were determined after extraction into n-heptane by gas–liquid chromatography (Varian 1400) using thermal conductivity detection [23].

Buffers

Krebs–Henseleit buffer pH 7.4 under constant aeration (95% oxygen–5% carbon dioxide) was used for preparation of slices. Krebs–Ringer–Hepes buffer pH 7.40 (ungassed) was used during incubation.

Chemicals

Human serum albumin (A1653) was purchased from Sigma Chemical Co., St Louis, Mo, U.S.A. Halothane was obtained from Ayerst Laboratories, New York, and Anaquest, Madison, Wi, supplied enflurane and isoflurane. Diazepam and prazepam were gifts from Hoffman–La Roche, NJ, and Warner–Lambert, Mi, respectively.

Statistics

Values are given as mean ± SEM. Experimental groups were compared by the Kruskall–Wallis analysis of variance. All standard curves were drawn by linear regression computation.

RESULTS

The presence of albumin in the incubations reduced the elimination of diazepam by the rat liver slices (figs 1–4). The reduction of diazepam elimination by albumin 1 mg ml^{-1} and 10 mg ml^{-1} after 2 h of incubation was 12% and 50%, respectively. The data were highly reproducible as the coefficients of variation for the four sets of experiments were 4%, 7% and 3% for control, albumin 1 mg ml^{-1} and 10 mg ml^{-1}, respectively.

In the absence of albumin, enflurane reduced the hepatic elimination of diazepam in a concentration-dependent manner (fig. 1). This reduction was only 8% at an enflurane concentration of 1.5 mmol $litre^{-1}$. No statistically significant changes were seen among the experimental groups in the presence of albumin 1 mg ml^{-1}. With albumin 10 mg ml^{-1}, however, a significantly increased elimination of diazepam was caused by enflurane. This increase was 24% at an enflurane concentration of 1.4 mmol $litre^{-1}$.

In the case of isoflurane (fig. 2), no statistically significant effect on the hepatic elimination of diazepam was observed under any of the experimental conditions. However, the experimental data followed a pattern similar to that of enflurane (fig. 1).

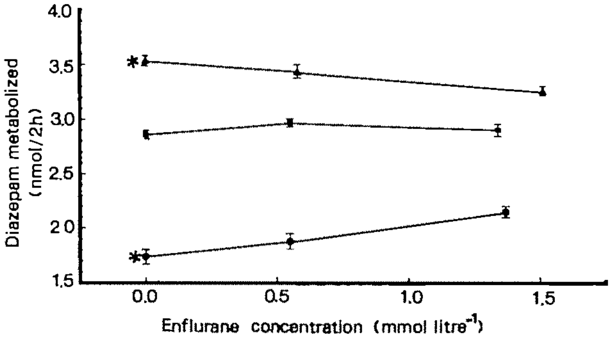

FIG. 1. The effect of enflurane on the elimination of diazepam by rat liver slices at 37 °C, with no albumin (▲), with albumin 1 mg ml^{-1} (■) or with albumin 10 mg ml^{-1} (●). Each point represents 10 incubation vials (two slices in each) from five separate livers. * Statistical significance along the x-axis ($P < 0.05$, Kruskall–Wallis analysis of variance).

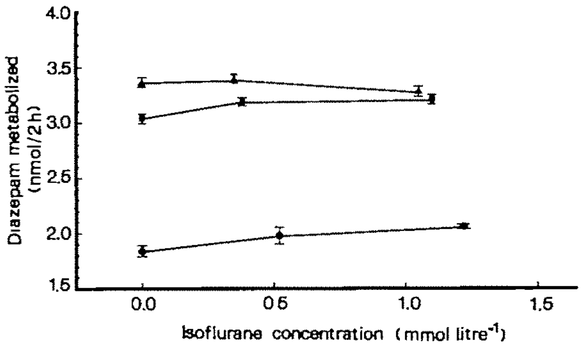

FIG. 2. The effect of isoflurane on the elimination of diazepam by rat liver slices at 37 °C, with no albumin (▲), with albumin 1 mg ml^{-1} (■) or with albumin 10 mg ml^{-1} (●). Each point represents eight incubation vials from four separate livers. No statistical significance along the x-axis.

Halothane (fig. 3) seemed to be the strongest inhibitor of the metabolism of diazepam in the absence of binding to albumin. This inhibition also was concentration dependent. The elimination of diazepam was reduced by 13% from control values at a halothane concentration of 1.0 mmol $litre^{-1}$. No statistically significant changes were seen when albumin 1 mg ml^{-1} was introduced, but a pattern similar to that of enflurane and isoflurane emerged (figs 1, 2). Halothane tended to cause increased elimination of diazepam at albumin concentrations of 10 mg ml^{-1}, although this was not statistically significant.

Trifluoroacetic acid, the metabolite of halothane, did not have any impact on the hepatic elimination of diazepam when no binding to

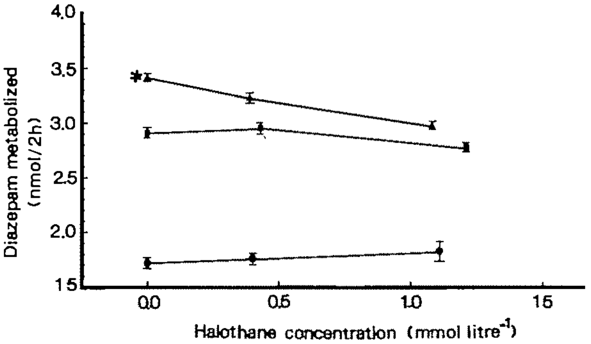

FIG. 3. The effect of halothane on the elimination of diazepam by rat liver slices at 37 °C, with no albumin (▲), with albumin 1 mg ml^{-1} (■) or with albumin 10 mg ml^{-1} (●). Each point represents eight incubation vials from four separate livers. * Statistical significance along the x-axis ($P < 0.05$, Kruskall–Wallis analysis of variance).

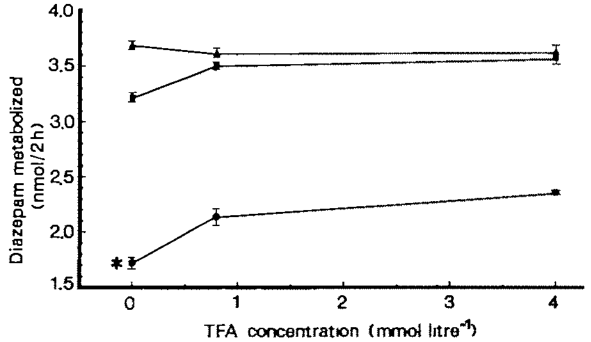

FIG. 4. The effect of trifluoroacetic acid on the elimination of diazepam by rat liver slices at 37 °C, with no albumin (▲), with albumin 1 mg ml^{-1} (■) or with albumin 10 mg ml^{-1} (●). Each point represents eight incubation vials from four separate livers. * Statistical significance along the x-axis ($P <$ 0.05, Kruskal–Wallis analysis of variance).

albumin occurred (fig. 4). The decrease of diazepam elimination caused by the presence of albumin 1 mg ml^{-1} was abolished by adding TFA. At the higher concentration of albumin (10 mg ml^{-1}) the elimination of diazepam was increased by 24% and 36% with TFA 0.8 and 4 mmol litre^{-1}, respectively. The apparently linear relationship between concentration of volatile anaesthetics and change in elimination of diazepam (figs 1–3) was thus not seen in the case of trifluoroacetic acid.

DISCUSSION

The present work indicates that the effect of protein binding on hepatic elimination of diazepam may be investigated by incubation of rat liver slices. Moreover, the effect of volatile anaesthetics on the two factors governing hepatic elimination of diazepam, enzyme activity and protein binding, may be assessed simultaneously. As hepatic elimination of diazepam is flow-independent, a closed incubation system is convenient for studying restrictively eliminated drugs such as diazepam.

Preincubation of slices for 30 min with diazepam establishes that only elimination resulting from biotransformation is measured, as distribution of diazepam to rat livers is achieved within 15 min [2]. Preincubation of the slices and transfer to new vials and buffer allowed for removal of the extraneous debris that is released from the slices by the cutting process. Although not proven, the preincubation is probably an important step in the achievement of experimental reproducibility. However, because isolated incubations in some experiments differed significantly from the mean of the remaining samples, non-parametric statistical analysis was applied.

Introducing human serum albumin to the incubation medium reduced the elimination of diazepam in a dose-dependent manner. This indicates that the *in vitro* hepatic uptake of diazepam is dependent on protein binding, which is compatible with studies on isolated livers [2] and its restrictive pattern of elimination in man [25].

Halothane proved to be the most potent inhibitor of diazepam biotransformation. This is in accordance with *in vivo* data reported in rat on mestranol and antipyrine [4, 8], while no such difference was found for verapamil in dogs [11]. Although the present study demonstrates that isoflurane may be the weakest agent in this respect, unequivocal data are not produced from the investigations cited above. Limited studies on halothane in man indicate that this agent inhibits the elimination of lignocaine during anaesthesia [7].

In vitro studies have shown that volatile anaesthetic agents displace drugs from binding sites on human serum albumin [15–17]. The data indicate that enflurane, in particular, is able to increase significantly the free fraction of diazepam. This is reflected clearly in the present work as enflurane, despite inhibiting the biotransformation of diazepam, increased its hepatic elimination when albumin was present. It follows that enflurane-induced displacement may be of greater pharmacokinetic significance than is enzyme inhibition, for the elimination of diazepam during anaesthesia. It also appears that halothane-induced displacement of diazepam affects its elimination as the inhibitory effect of the agent on the eliminating enzymes is blunted by the presence of albumin.

It is concluded that volatile anaesthetic agents may cause pharmacokinetic drug interactions by acting on both enzyme activity and protein binding. This study has confirmed previous observations that halothane is a stronger inhibitor of drug metabolizing enzymes than are the other volatile agents. The observation that volatile anaesthetics, particularly enflurane, displace drugs such as diazepam from serum protein binding sites is supported. In the case of enflurane its action on drug protein binding may be more important for hepatic drug elimination than inhibition of enzyme activity.

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EFFECTS OF SOUNDS PRESENTED DURING GENERAL ANAESTHESIA ON POSTOPERATIVE COURSE

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SUMMARY

In a double-blind, randomized study, patients undergoing cholecystectomy were administered one of four different sounds during general anaesthesia: positive suggestions, nonsense suggestions, seaside sounds or sounds from the operating theatre. The effect of these sounds on the postoperative course was examined to assess intraoperative auditory registration. No differences were found between the four groups in postoperative variables.

There is evidence that patients under general anaesthesia can register sounds present during operation [1–3]. Recall of these sounds is termed "awareness" [4]. Experimental studies in which auditory stimuli were administered to patients during surgery confirmed such registration via postoperative interviews, recall and recognition tests [5–7], postoperative hypnosis [8] and postoperative non-verbal responses [9, 10]. Peroperative registration of sounds has been examined *indirectly* in other studies, by presenting positive suggestions to patients during operation and studying their possibly beneficial effect on the postoperative course. However, these studies were poorly designed. Wolfe and Millet [11] and Hutchings [12] did not use control conditions, Pearson [13] compared patients without controlling the nature of the surgical procedure, and in the study of Abramson, Greenfield and Heron [14] small sample sizes were used.

In a more recent study [15] these design faults were avoided. In a double-blind, randomized study, positive suggestions, noise or sounds from the operating theatre were presented to three groups of patients undergoing cholecystectomy with or without choledochotomy during general anaesthesia. Older patients ($\geqslant 55$ yr) who received positive suggestions had a significantly shorter postoperative hospital stay than the other patients in this age category.

After preliminary results of this study [16] a replication was initiated, with some adjustments. These included the provision that each patient, while anaesthetized, would receive the same uniform "filler" sound before and after the presentation of the experimental sounds. In this way, the patients would be shielded from other sounds that might reach them during these periods of less deep anaesthesia. Furthermore, a fourth condition was added: the administration of nonsense suggestions, in order to examine whether intonation alone is sufficient to produce an effect or whether the verbal content of the positive suggestions is relevant. Also, a more neutral noise was chosen than that used by Bonke and colleagues [15]. The aim of the present study was to assess intraoperative auditory registration by examining the effect of different sounds administered during general anaesthesia on postoperative course.

PATIENTS AND METHODS

Patients

Dutch speaking patients, awaiting elective cholecystectomy in a 3-year period between April 1982 and April 1985, were studied. Patients with hearing impairment and those from psychiatric

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hospitals were excluded. One hundred and six patients (36 male) aged 19–86 yr (mean 53.3 ± 14.9 (SD) yr) gave informed consent to take part in the study. The investigation was approved by the local Medical Ethics Committee.

Anaesthesia

Premedication comprised either fentanyl–droperidol (Thalamonal) 1–2 ml i.m. 1 h before surgery or lorazepam 2 mg orally 2 h before surgery, and atropine sulphate 0.25–0.50 mg i.m. Anaesthesia was induced with thiopentone, and suxamethonium was given to facilitate intubation of the trachea, after which the lungs of the patients were ventilated with 67% nitrous oxide in oxygen. During surgery fentanyl was given and pancuronium was administered for muscle relaxation. When indicated by clinical signs of inadequate anaesthesia, enflurane was given.

Procedure

Before operation patients were assigned randomly to one of four groups. In the first group (PS), a tape with two repeated fragments containing positive suggestions was played continuously. These fragments suggested relaxation, well-being, a pleasant feeling in every respect and absence of nausea and vomiting, and predicted a good recovery. The first fragment (220 s)—spoken by a woman—addressed the patient directly, for example: "You are completely relaxed...after the operation you will feel fine and comfortable, and you will heal quickly...". The second fragment (40 s)—spoken by a man—commented on the patient's state and presumed recovery: "Great... that looks excellent...very good indeed...This patient will soon be cured and able to go back home...." (The exact text of the positive suggestions, similar to that used by Bonke and colleagues [15], can be obtained from the first author.) After each fragment 95 s of seaside sounds was presented. The 30-min tape comprised fragment 1 for 49%, fragment 2 for 9% and seaside sounds for 42% of its duration.

In the second group (NS), a tape containing nonsense suggestions interspersed with seaside sounds was played. Nonsense suggestions were created by filtering the above mentioned positive suggestions, in such a way as to make the content of the suggestions incomprehensible while retaining the intonation. The sequence and duration of the fragments on this tape were identical to those of the tape in the first group.

In the third group (SS), a tape with only seaside sounds was played.

In the fourth group (OT), patients were exposed to the sounds audible during the operation that were picked up by a microphone.

All sounds were administered during the surgical procedure from the initial incision until the beginning of closure of the peritoneum. All patients were administered the seaside sounds, as filler sound, from intubation until the initial incision and from the beginning of closure of the peritoneum until the nitrous oxide was discontinued.

The procedure used to present the sounds was the same as that applied by Bonke and colleagues [15].

Apparatus

An automatic reverse cassette recorder (UHER-CR 210) was used to administer the sounds of the tapes. For the presentation of operating theatre sounds, a microphone (Sennheiser MD-421-U-4) was attached to the operating table adjacent to the head of the patient and connected to the input of an amplifier. The amplifier was so adjusted that the sound level presented to the patient via the earphones was the same as would have been present at the external auditory meatus under normal circumstances. During all experiments both sounds picked up by the microphone and the sounds from the cassette recorder were fed into the amplifier (fig. 1). The output of the amplifier was transmitted to the patient through earphones (UHER-W214). A switch on the amplifier determined which sound would be audible through the earphones. No one

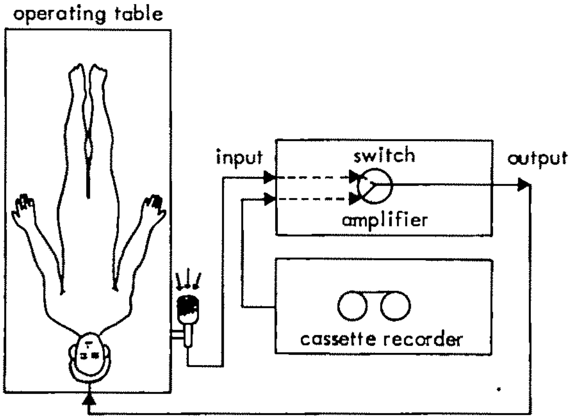

FIG. 1. Design of apparatus used in the study.

in the operating theatre, including the investigator, knew the group to which a patient had been assigned.

Measurements

The postoperative course was evaluated by means of the following variables: pain, subjective well-being, nausea and vomiting, evaluation by the nursing staff, and duration of postoperative hospital stay. On the 3rd day after operation (day of surgery = 0), five 5-point rating scales (RS I–V) were administered:

For pain (RS I). "Did you have much pain yesterday?" No, none or hardly any = 1; yes, very much = 5.

For subjective well-being. "How did you feel yesterday?" RS II: Very well = 1; very bad = 5. RS III: Very relaxed = 1; very tense = 5. RS IV: Healthy = 1; very ill = 5.

For nausea and vomiting (RS V). "Did nausea or vomiting give you any trouble yesterday?" No trouble = 1; yes, a lot of trouble = 5.

On day 6, a semistructured interview was conducted by the "blind" investigator (S.B.) to evaluate pain, subjective well-being, and nausea during the 6 preceding days. These variables were then scored on three 3-point rating scales: from no pain = 1 to much pain = 3; from good = 1 to bad = 3; and from no nausea = 1 to much nausea = 3, immediately after the interview. In addition, the patient was asked: "Were you having any experiences while you were asleep during the operation?"

On the same day, the nursing staff evaluated the postoperative recovery of the patient to date on a 3-point rating scale, from good = 1 to bad = 3.

The following variables were obtained from the patient's hospital chart: amount of postoperative analgesic received (no more medication (0) or more medication (1) than a pre-set base amount); volume of nasogastric suction or drainage (Fluid I) and fluid lost through vomiting (Fluid II) in the 6 days following the operation. Duration of postoperative hospital stay was registered after discharge.

Statistical analysis

Before statistical analysis, the number of variables referring to pain, subjective well-being and nausea and vomiting was reduced. The scores on these variables were recoded first (table I), then those variables which assessed the same aspect of recovery were combined into PAIN (RS I, interview score and analgesics), WELLB (RS II, RS III, RS IV and interview score) and NAUSEA (RS V, interview score, Fluid I and Fluid II). Three values were attached to these combined variables: *favourable*, if all constituent parts scored 1; *unfavourable*, if at least one part scored 3; *medium*, in the remaining cases.

The Chi-square test for contingency table and the Kruskal–Wallis non-parametric test were used to evaluate differences between the four groups.

RESULTS

There was no recall of any event.

The following variables were treated as patient characteristics: sex, age, ward, number of previous operations, level of experience of the surgeon (hi = senior surgeon, lo = junior surgeon), ASA grade, premedication, addition of enflurane, duration of operation (from initial incision to closure of the peritoneum) and amount of blood loss.

There were no statistically significant differences or trends between groups with respect to these characteristics (all P values > 0.15) (table II).

Between groups, no significant differences in any of the five dependent variables (PAIN, WELLB, NAUSEA, nursing staff evaluation score, postoperative hospital stay) were demonstrated (table III).

DISCUSSION

The results do not clarify the issue of intraoperative auditory registration. On day 6, none of the patients remembered having registered sounds during the operation. Between the groups, no statistically significant difference in postoperative variables was found; this may be explained by various considerations.

TABLE I. *Recoded scores of the variables relating to pain, subjective well-being and nausea and vomiting.* † *Trisection based upon percentiles of cumulative frequency distribution*: P_{33} = *160 ml*; P_{67} = *361 ml.* ‡ *Dichotomized upon cumulative frequency distribution (median = 0 ml)*

Variables	1	2	3
5-point rating scale for RS I–V	1 , 2	3	4 , 5
Analgesics	0		1
Fluid I (ml)†	⩽ 160 ml	161–360 ml	⩾ 361 ml
Fluid II (ml)‡	0 ml		> 0 ml

TABLE II. *Patient characteristics.* n = *Total number of patients in each group. Top part of table: distribution of numbers (percentages) of patients; test statistic = chi-square for contingency table. Lower part of table: median values; test statistic = chi-square based upon Kruskal–Wallis non-parametric test corrected for ties. PS = positive suggestions; NS = nonsense suggestions; SS = seaside sounds; OT = operating theatre sounds*

	PS ($n = 24$)	NS ($n = 26$)	SS ($n = 27$)	OT ($n = 29$)	χ^2	df	P
Sex							
M	10 (42)	9 (35)	10 (37)	7 (24)	2.00	3	0.57
F	14 (58)	17 (65)	17 (63)	22 (76)			
Ward							
I	15 (63)	20 (77)	21 (78)	21 (72)	1.84	3	0.61
II	9 (38)	6 (23)	6 (22)	8 (28)			
Experience of surgeon							
Hi	9 (38)	7 (27)	8 (30)	9 (31)	0.70	3	0.87
Lo	15 (63)	19 (73)	19 (70)	20 (69)			
Premedication							
Thalamonal	21 (87)	20 (77)	18 (67)	18 (62)	5.02	3	0.17
Lorazepam	3 (13)	6 (23)	9 (33)	11 (38)			
ASA grade							
I	13 (54)	11 (42)	17 (63)	13 (45)	8.16	6	0.23
II	9 (38)	15 (58)	7 (26)	12 (41)			
III	2 (8)	0 (0)	3 (11)	4 (14)			
Enflurane							
Yes	8 (33)	6 (23)	8 (30)	9 (31)	0.72	3	0.87
No	16 (67)	20 (77)	19 (70)	20 (69)			
Age (yr)	55.0	58.0	50.0	55.0	3.39	3	0.33
Previous surgery	1	1	1	2	4.07	3	0.25
Duration of operation (min)	72.5	65.0	55.0	60.0	3.34	3	0.34
Blood loss (ml)	252.5	197.5	195.0	220.0	2.38	3	0.50

TABLE III. *Dependent variables.* n = *Numbers of patients in each group. Distribution of numbers (percentages) of patients, and median values of a variable, in each group.* † *One patient omitted (extra medication).* ‡ *One patient omitted (no Nausea interview score). PS = Positive suggestions; NS = nonsense suggestions; SS = seaside sounds; OT = operating theatre sounds.* WELLB = *Wellbeing*

	PS ($n = 24$)	NS ($n = 26$)	SS ($n = 27$)	OT ($n = 29$)	Test statistic	df	P
PAIN							
Favourable	7 (29)	2 (8)	6 (22)	2 (7)			
Medium	11 (46)	13 (50)	9 (33)	11 (38)	$\chi^2 = 9.80$	6	0.13
Unfavourable	6 (25)	11 (42)	12 (44)	16 (55)			
WELLB							
Favourable	5 (21)	2 (8)	2 (7)	3 (10)			
Medium	10 (42)	8 (31)	12 (44)	9 (31)	$\chi^2 = 5.46$	6	0.49
Unfavourable	9 (38)	16 (62)	13 (48)	17 (59)			
NAUSEA							
Favourable	4 (17)†	2 (8)†	5 (19)	4 (14)‡			
Medium	9 (39)	7 (28)	4 (15)	8 (29)	$\chi^2 = 5.25$	6	0.51
Unfavourable	10 (44)	16 (64)	18 (67)	16 (57)			
Nursing staff evaluation score							
1	12 (50)	15 (58)	15 (56)	13 (45)			
2	11 (46)	10 (38)	12 (44)	15 (52)	$\chi^2_{KW} = 1.15$	3	0.76
3	1 (4)	1 (4)	0 (0)	1 (3)			
Postoperative hospital stay (days, median)	10	10	9	10.5	$\chi^2_{KW} = 1.99$	3	0.57

In the present study, it was assumed that suggestions can influence postoperative variables. However, if such an effect indeed occurs, it remains uncertain which aspects of the suggestions are effective. The positive suggestions affected postoperative hospital stay in the study of Bonke and colleagues [15], but did not do so in the present study. This difference may be attributed to the fact that both fragments of positive suggestions were spoken by men in the study by Bonke and colleagues, whereas in the present study fragment 1 was spoken by a woman. A male voice instead of a female voice may have a different effect on postoperative recovery, because of the greater authority attributed to men in medical situations.

It is possible that the four sounds administered during surgery did not differ sufficiently to produce different effects on the postoperative variables. The positive suggestions and the nonsense suggestions had the same intonation; in the postoperative interview, all patients (upon being asked) considered seaside sounds to be neutral or positive; the sounds from the operating theatre proved to be perceived as less negatively toned and less life-threatening than had been anticipated.

Furthermore, the ability of the chosen variables to reflect subtle effects may be questioned. With regard to postoperative hospital stay, a difference between the present study and that of Bonke and colleagues [15] can be found in the lower degree of sensitivity of the duration of hospital stay as a measure. This may have diminished the possibility of differentiation between groups. In the present study, this variable had a lower average score than the one Bonke noted 4 years earlier (mean = 10.9, SD = 3.6 and mean = 12.9, SD = 3.3, respectively).

Finally the number of patients under study may have been too small to determine small differences in effect on the postoperative variables of the groups.

In the study of Bonke and colleagues [15], two of three groups under study were pooled (OT sounds and Noise) without testing separately the postoperative hospital stays of the older of these groups of patients, in particular. Furthermore, Bonke failed to take account of the extra surgical procedure, choledochotomy, which may have influenced their results, since choledochotomy entails a greater trauma for the patient and demands a longer minimal duration of postoperative hospital stay than does cholecystectomy alone.

Studies of indirect evidence of intraoperative auditory registration by examining the effect of different sounds fed in during general anaesthesia on postoperative criteria are ambitious. This type of clinical study is based on too many assumptions. The phenomenon of intraoperative auditory registration may be studied better by postoperative retrieval of information fed in during general anaesthesia, by using highly sensitive memory tests.

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PREDICTING SUCCESSFUL BRACHIAL PLEXUS BLOCK USING CHANGES IN SKIN ELECTRICAL RESISTANCE

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G. M. ARTHURSON, D. A. ROBINSON AND G. D. CROSS

SUMMARY

Skin electrical resistance is determined by the degree of sweating of the skin which is, in turn, related to sympathetic nervous system activity in the area concerned. It is increased when the nerves supplying the area are damaged or blocked by local anaesthetic agents. We have assessed the temporal and spatial relationship between the onset of sympathetic and sensory loss in the hand following brachial plexus block in 44 patients. Skin electrical resistance, measured using a simple ohm meter, has been shown to increase within 2 min of brachial plexus blockade with 1% lignocaine and adrenaline 1:200000. This increase is an early and reliable indicator of subsequent, and occasionally delayed, sensory loss.

Blockade of the brachial plexus provides ideal conditions for upper limb surgery and avoids the problems and complications of general anaesthesia. However, anaesthesia following brachial plexus block is occasionally incomplete and success may not be predicted with confidence for a considerable time after the injection of local anaesthetic. The traditional method of assessing the degree of anaesthesia produced by brachial plexus block is based on the repeated use of a painful stimulus, usually pinprick. If sensation is intact, this may be unpleasant and may rapidly destroy patient confidence. Results obtained by these means are subjective and may be difficult to interpret if inconsistent, or if patient co-operation is poor. If the block fails, or is inadequate, further time is required to establish general anaesthesia or a suitable alternative technique. A simple early non-invasive predictive test of success would allow brachial plexus block to be used with greater confidence.

The palmar surfaces of the hands and feet have a reduced skin electrical resistance (SER) compared with the rest of the body [1]. The actual value of skin electrical resistance depends upon the activity of the sympathetic nervous system and is a direct result of changes in the degree of skin sweating. Skin electrical resistance is reduced as body temperature increases and is increased during sleep or when body temperature decreases. Following thoracic sympathectomy, these changes are not observed and the resistance remains high [2]. Skin electrical resistance also increases following traumatic damage to, and local anaesthetic block of, peripheral nerves [3] and, under these circumstances, geographically identical areas of analgesia and increased skin electrical resistance are demonstrated. The correlation between loss of sensation and loss of sweating, associated with changes in skin electrical resistance, has been confirmed for a variety of nerve injuries [4,5] using various techniques [4–9].

This study was designed to establish whether success could be predicted, soon after brachial plexus block, from changes in the skin electrical resistance of the hands.

PATIENTS AND METHODS

Forty-four patients, scheduled to undergo routine and emergency hand surgery under brachial

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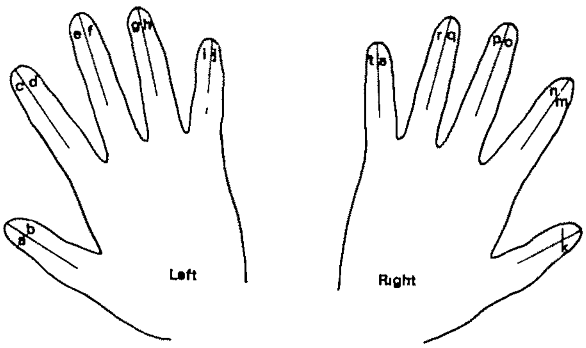
A: Block of left brachial plexus



B: Block of right brachial plexus.

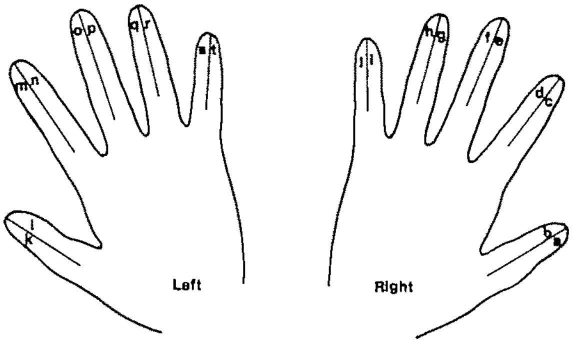


FIG. 1. Sites a–t at which skin electrical resistance measurements and sensory tests were made.

plexus block, were studied. Informed consent was obtained from all patients and approval for the study was granted by the hospital ethics committee. Patients deemed unsuitable for a regional technique and those with a chronic peripheral neuropathy were excluded. Anxious patients received premedication with a benzodiazepine by mouth.

On arrival of the patient in the anaesthetic room, baseline recordings of sensation to pinprick and measurements of skin electrical resistance were obtained from each hand as follows:

(a) The presence (P) or absence (A) of sensation to pinprick over the medial and lateral aspects of all accessible digit tips of each hand was recorded. Data were obtained from each of 20 sites, a–t, shown in figure 1. Sites a–j always identified the 10 test sites on the digits of the arm which was to undergo brachial plexus blockade. Further recordings of pinprick sensation were made 10, 20 and 30 min after completion of a brachial plexus block. Sample sites that were inaccessible or those known to have suffered acute neuronal damage were excluded from the study, as it is known that SER is increased in these circumstances.

(b) Measurements of skin electrical resistance (MΩ) were obtained over the medial and lateral aspects of all accessible digit tips of each hand (fig. 1). Skin electrical resistance was measured using a hand-held probe [10] with two isolated, lead-coated electrodes 1 cm apart at the probe tip (fig. 2). A force of 2.5 N was required to depress the spring-loaded shaft of the probe fully, before the activation of a switch, thus ensuring a standard pressure at the probe–skin interface. The resistance between the two electrodes was displayed on a digital readout ohm meter, with a range of 0–20 MΩ for patients 1–31 (group 1) and 0–200 MΩ for patients 32–44 (group 2). Each ohm meter was powered by a 9-V battery and had dimensions of 78 × 110 × 20 mm. Further recordings of skin electrical resistance were made 2, 4, 6, 8, 15 and 30 min after the completion of a brachial plexus block. Resistance was not recorded from sample sites that were inaccessible or from those known to have suffered acute neuronal damage.

Following the recording of baseline measurements, a brachial plexus block was performed on all patients using the supraclavicular approach described by Moore [11]. Thirty millilitre of 1% lignocaine with adrenaline 1:200000 was deposited in the region of the plexus after the demonstration of paraesthesia. If paraesthesia was not obtained, but the subclavian artery inadvertently contacted, local anaesthetic was placed around and lateral to the artery. In the event of neither of these occurrences, local anaesthetic was distributed in the region of the plexus as indicated by standard landmarks.

The success of each supraclavicular block was classified as full, partial or absent. A full block occurred when pinprick sensation was absent in all of the sites a–j. Partial block occurred when pinprick sensation remained in one or more of the sites a–j, 30 min after the injection of the lignocaine. Supplementary anaesthesia was given to any patient in whom regional anaesthesia was insufficient for the safe and comfortable conduct of surgery. (A partial block did not necessarily indicate a need for supplementary anaesthesia.)

Statistical analysis of data

Statistical analysis of data in this study was made using unpaired *t* tests on the Statistical

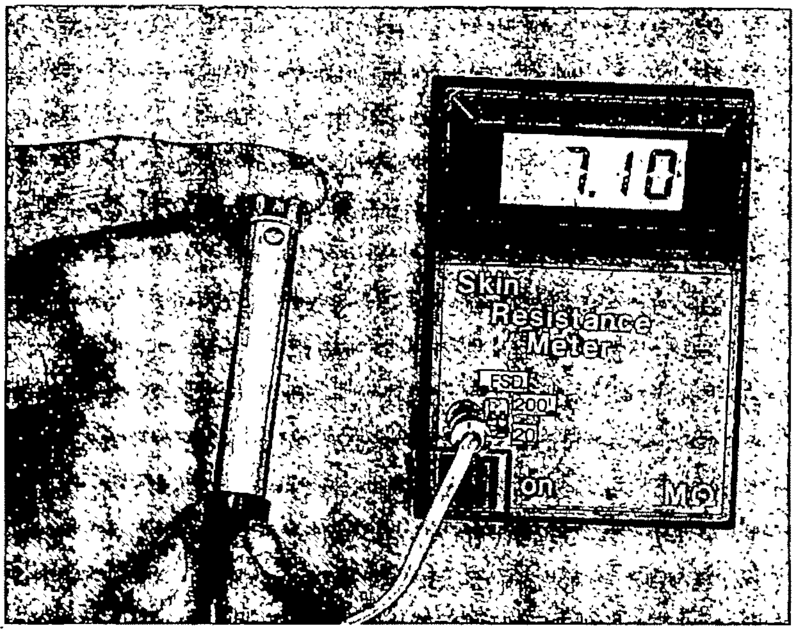


FIG. 2. Digital-readout ohm meter with hand-held probe.

Analysis System under MVS/TSO run on an IBM 4341 computer at Yale University, Connecticut, U.S.A.

RESULTS

Forty-four patients were studied, 31 in group 1 and 13 in group 2. Patient data and information concerning the success of the brachial plexus blocks are given in table I. Eighty-five percent of blocks were satisfactory for the completion of surgery.

The maximum number of skin electrical resistance recordings possible was 4960 in group 1 and 2080 in group 2. Data were obtained on 4479 occasions (90.3 %) in group 1 and 1992 occasions (95.8 %) in group 2. Absent fingers or the presence of acute wounds or dressings prevented the recording of data on 263 occasions in group 1 and 48 occasions in group 2. Data were not recorded on the remaining occasions because of other technical difficulties.

In order to determine the predictive value of the skin electrical resistance readings, the sample sites a–j for a given patient were classified into those which, at 30 min after brachial plexus block, demonstrated either full anaesthesia (A) or continued to have sensation to pinprick (P). Sites on the limb which had not undergone block, that is k–t, were categorized as controls (C). For each classification (A, P or C), an average value of skin electrical resistance was calculated for each patient at each time interval (0, 2, 4, 6, 8, 15 and 30 min). A final mean value (mA, mP and mC) for each time interval was determined for each classi-

TABLE I. *Demographic data relating to patients in groups 1 and 2. GA = General anaesthesia*

	Group 1 ($n = 31$)	Group 2 ($n = 13$)
Female/Male	10/21	7/6
Mean age (yr)	53.5±17.2	51.7±22.1
Emergency patients	9	4
Non-emergency	22	9
Right handed	29	12
Left handed	2	1
Block on RIGHT	17	10
Block on LEFT	14	3
Premedication given	8	8
No premed. given	23	5
Paraesthesia obtained	22	12
No paraesthesia obtained	9	1
Full block obtained	17	10
Partial block obtained	11	2
No block obtained	3	1
GA required	6	1
GA not required	25	12

TABLE II. *Comparison of mean grouped values of skin electrical resistance (SER) (MΩ) for areas a–j in which sensation was absent at 30 min after the block (mA), areas a–j in which sensation was present at 30 min (mP) and control areas a–t (mC).* *$P < 0.05$; **$P < 0.01$; ns = $P > 0.05$

				Statistical significance		
Time (min)	mA	mP	mC	mA+mP	mP+mC	mA+mC
Group 1						
0	6.7±4.7	5.0±3.9	6.0±4.0	ns	ns	ns
2	9.0±6.1	5.9±5.0	5.7±4.0	ns	ns	*
4	10.5±5.4	6.7±5.2	6.4±4.1	*	ns	**
6	12.6±5.6	7.7±5.2	6.8±4.2	**	ns	**
8	13.4±5.9	9.6±6.0	7.2±4.9	ns	ns	**
10	14.5±5.7	8.6±5.3	7.3±4.6	**	ns	**
15	15.5±5.4	9.3±4.4	7.1±4.1	**	ns	**
30	16.3±4.2	10.1±3.4	6.9±4.3	**	*	**
Group 2						
0	13.4±10.6	5.6±2.0	10.0±8.5	ns	ns	ns
2	22.3±16.0	6.1±0.6	9.3±7.0	ns	ns	*
4	33.4±23.6	5.6±1.3	11.5±8.8	ns	ns	**
6	46.2±28.1	5.5±0.7	12.3±8.6	ns	ns	**
8	52.2±28.4	5.6±1.3	11.4±7.0	*	ns	**
10	62.0±30.1	7.6±0.2	12.7±7.2	*	ns	**
15	63.9±31.2	7.2±2.6	11.9±7.0	*	ns	**
30	75.0±29.4	8.4±5.1	18.3±19.7	**	ns	**

fication, calculated from the average skin resistance values obtained from all of the individual patients. For each time interval the values of mA, mP and mC were compared using unpaired *t* tests (table II).

The results show that there was no statistically significant difference in skin electrical resistance between the two hands before the performance of the brachial plexus block. However, following the block, there was a steady increase in those areas which subsequently became anaesthetized. In those areas of the blocked hand where no change in sensation occurred the increase in resistance was smaller.

Further analysis of the data revealed that a significant difference in skin electrical resistance existed, between those areas which subsequently became anaesthetic at 30 min and those that did not (mA, *v.* mP). This difference was apparent 4 min after the injection of lignocaine in group 1 and after 8 min in group 2. A comparison of mean skin electrical resistance values from areas which subsequently became anaesthetic with those from control areas (mA *v.* mC) demonstrated a significant difference as early as 2 min after blockade in groups 1 and 2.

An analysis of the data from the three patients in group 1 in whom the brachial plexus block failed totally to produce a somatic block revealed no statistically significant change in the resistance values when compared with the control areas (table III).

DISCUSSION

The potential for the use of changes in skin electrical resistance as an early guide to the success of a brachial plexus block is based on the selective action of local anaesthetics on different nerve fibres. The function of unmyelinated postganglionic sympathetic C fibres is blocked in advance of the myelinated Aδ fibres in a mixed peripheral nerve. Therefore, a reduction in sym-

TABLE III. *Comparison of mean grouped values of skin electrical resistance (SER) (MΩ) for areas a–j (mP) and k–t (mC) in three patients in group 1 in whom the brachial plexus block failed totally. No significant difference between mP and mC* ($P > 0.05$)

Time (min)	mP	mC
0	5.0±2.1	5.6±3.4
2	4.7±2.4	4.9±4.3
4	5.8±3.7	5.3±4.3
6	6.0±3.6	5.8±4.0
8	7.0±3.9	5.3±4.2
10	7.3±4.5	5.3±4.2
15	7.4±4.8	5.9±4.2
30	7.0±3.7	5.7±4.8

pathetic activity to an arm could be expected to herald a subsequent sensory or motor block following brachial plexus anaesthesia.

Analysis of our results confirmed an early alteration in skin electrical resistance in areas where sensory loss occurred subsequently. Significant changes were detected after 2 min when compared with the control hand, although when compared with unblocked areas on the same hand, discrimination was delayed slightly, to between 4 and 8 min. We can conclude, therefore, that this technique is suitable for the early prediction of a successful sensory block.

The ability of the skin electrical resistance to determine which areas would subsequently become anaesthetic appears to be less precise if comparisons are made within the same hand rather than with the control hand. This suggests that, 30 min after a block, the function of some autonomic fibres in the "block" arm has been suppressed without alteration of the somatic supply to the same area. There may be two reasons for this: first, that the sympathetic supply to the arm is not dermatomal and that there is considerable overlap in the sympathetic supply to the skin; second, that, sympathetic fibres are blocked but the corresponding sensory fibres are not. The latter might imply that, given sufficient time, the sensory fibres in this region might also become anaesthetized.

Richter [3], studying the ulnar nerve, stated that the margin between areas of high and low skin electrical resistance was sharp and followed the distribution of the blocked or damaged nerve. In general terms, we are unable to confirm this, possibly because we studied the brachial plexus rather than an isolated peripheral nerve. The brachial plexus, unlike the ulnar nerve which is isolated from other neural tissue at the elbow, is formed of large numbers of fibres destined for many somatic areas. These are eventually spread widely within the limb and endow the potential for differences in diffusion of local anaesthetic in a non-uniform manner throughout the plexus.

Although we used two different ohm meters in our study, it was not our intention to compare their function; an ohm meter with a wider range became available for use with group II patients. However, it is apparent, from the baseline values of skin electrical resistance, that either there was a slight difference in the function of the two ohm meters used in our study or the two groups were not, in fact, from the same population. However, the trend of results in both groups is identical and statistical significance occurs at similar points for each group. The explanation of these minor differences is difficult to document, but may have arisen as a result of an inherent difference in sensitivity within the ohm meters. The use of a machine with a wide measurement range, as in group 2, is to be encouraged as it allows greater separation of values of skin electrical resistance from "blocked" and "unblocked" areas.

Although we have documented a definite statistical significance between blocked and unblocked areas, we find it difficult to give any definite guidelines concerning the sort of value which would indicate loss of sensation. However, as a rough guide, a value of skin electrical resistance in excess of 20 MΩ appears to have been a fair prognostic indicator. This is in keeping with the results obtained by Wilson [5], using the first of our machines, which showed that a resistance of 20 MΩ in combination with absence of sensation to pinprick was consistent with complete division of a digital nerve. One point that is of great importance is that, in none of our study patients in whom the brachial plexus block failed, did the skin electrical resistance increase from control values. This indicates that failure of the resistance to increase from control values within 8 min of the completion of a brachial plexus block confirms an unsuccessful block.

Local anaesthetic blocks occasionally take a considerable amount of time to have full effect. The practice of continually testing skin sensation using a pin is unpleasant for the patient and rapidly destroys patient confidence if sensation is intact. The testing of sensory loss contains a highly subjective element and is, therefore, sometimes extremely difficult in the elderly, confused, young or unco-operative patient. In contrast, the measurement of skin electrical resistance is an easily performed objective test which is not distressing and requires little patient co-operation. Common clinical contaminants make very little difference to the measurement of skin electrical resistance [10] and, although premedication may affect values slightly, the almost certain presence of a control limb for comparison makes the use of skin electrical resistance testing simple and reliable.

In conclusion, we have documented that changes in skin electrical resistance occur rapidly after successful brachial plexus blockade and are an accurate guide to the onset of analgesia. Failure of skin electrical resistance to increase indicates a failed block and, for this reason, the testing of skin electrical resistance may be a more pleasant method of continual assessment of sensory loss. The technique may have indications where the need to eliminate subjective assessment of sensory block is important.

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THE PHYSICS OF LASERS AND IMPLICATIONS FOR THEIR USE DURING AIRWAY SURGERY

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In 1917, Albert Einstein recognized the existence of stimulated emissions [21]. The first description of stimulated optical emission of monochromatic light using ruby as the active material—the ruby laser—was provided by Theodore Maiman in 1960 [45]. The more powerful neodymium-in-glass laser was discovered a year later. It was hoped that lasers would be useful in medicine for the excision of tumours, but initial expectations were not realized. Their poor absorption by non-pigmented tissues necessitated the use of large amounts of energy, with the result that the thermal effect could not be localized to diseased tissue [80].

In 1966, at the American Optical Corporation Laboratories, Yahr and Strully discovered that the carbon dioxide (CO_2) laser can cut tissue [103]. Strong and Jako first appreciated the potential of the CO_2 laser for use in otolaryngology in 1971 [87]. The development of the micromanipulator by Polanyi in 1974, enabling the CO_2 laser to be used with an operating microscope, greatly facilitated its use for microlaryngeal surgery [63]. The argon laser has been used extensively in ophthalmic surgery and dermatology since about 1970 [16], and the neodymium-in-yttrium-aluminium-garnet (Nd–YAG) laser was first introduced in 1975 for the endoscopic treatment of gastrointestinal haemorrhage [37].

A knowledge of the physical properties of lasers enables a better understanding of their application in surgery and is essential for the implementation of effective safety measures. The fundamental physics of medically used lasers, and the hazards of their use, will be presented. The anaesthetic implications and management of laser surgery of the upper airway is emphasized. The complications of laser usage and the precautionary measures to minimize them are discussed and likely future developments in laser surgery are outlined. The following discussion of the physics of lasers and their applications is a simplification; the interested reader is directed to two reference works on the subjects [4, 47].

Laser physics

Lasers are intense sources of electromagnetic radiation. The word LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. The terms "light" and electromagnetic radiation are used interchangeably in this discussion, although not all lasers operate in the visible range of the spectrum. The electromagnetic description of "light" enables one to understand the characteristics of laser "light", including its monochromatic nature, temporal and spatial coherence, and collimation. This "light" is of one wavelength and the waves travel in phase and parallel across a wavefront. In contrast, conventional light sources emit light of varying wavelengths in all directions. According to Bohr's theorem, the electrons of an atom can be imagined to circle the nucleus in discrete orbits; the orbits populated by the electrons determine the energy level of the atom. Radiation is absorbed or emitted when electrons are transferred from one orbit to another. The frequency of the radiation emitted or absorbed is related to the energy difference of the two states according to the Bohr formula, $E = hV$, where E is the energy difference between two energy levels, h is Planck's constant and V is frequency. The basis of the quantum theory is that energy exists in discrete packages, quanta or photons. Atoms, molecules and ions

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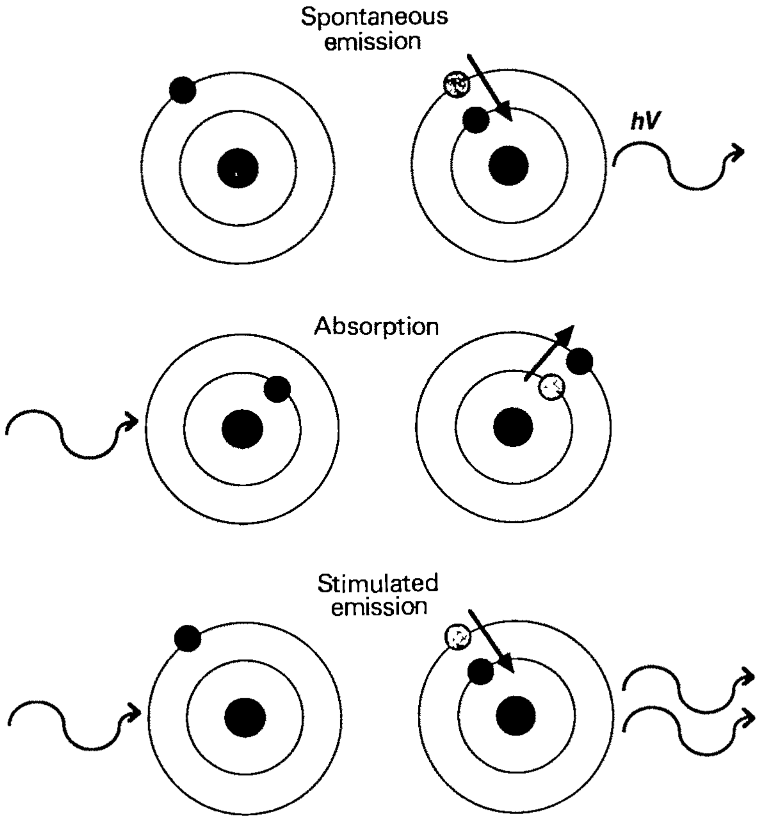

FIG. 1. The three processes of radiation.

undergo transition from a higher to a lower energy state with the emission of a photon as the electron drops from a higher orbit to a lower one in the case of an atom, or as a molecule changes from one vibrational state to another as, for example, in the carbon dioxide molecule. An atom or any other quantum system tends to move from a higher to a lower energy state by spontaneous emission of discrete amounts of radiation; spontaneous emission is propagated in any direction. Conversely, when an atom, molecule or ion at a lower energy level is exposed to specific amounts of radiation, it may absorb that energy and be "excited" with an electron raised to a higher orbit or a molecule changed to a different rotational or vibrational state.

When, during stimulated emission, an atom in an excited state is exposed to the radiation (photonic energy) of a frequency matching the energy difference between two orbits (excitation energy), the atom can then emit the newly "absorbed", in addition to the existing, amount of "excited" energy by return of its electron to the lower level. Two photons are then emitted—the injected photon plus the photon emitted by the electron returning to the lower orbit; the atom reverts, thereby, to its lower energy level (fig. 1). The two emitted photons have the same energy level (*hV*), frequency, phase and direction or, in other words, the *stimulated* radiation has the same frequency, phase and direction as the *stimulating* radiation. The *stimulating* radiation has thus been amplified. For a predominance of stimulated emission to occur, a large majority of atoms need to be in a higher energy, or excited state rather than a lower state, in order to compensate for the loss of photons that escape without participating in the process. The resulting condition is called a population-inversion, because normally the higher energy levels of atoms, ions or molecules are less populated than the lower ones. In fact, spontaneous emission is minimized by maintaining the population-inversion. The method by which the higher energy levels are achieved is

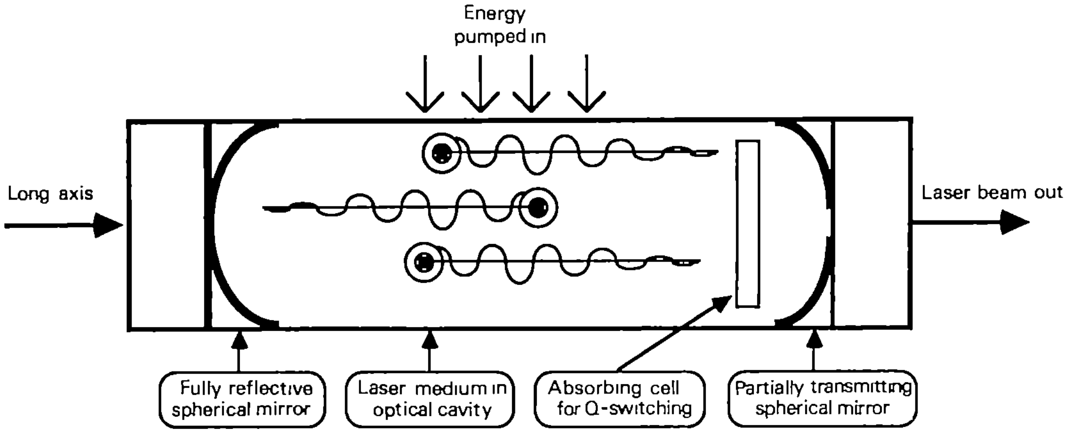
Energy pumped in
Long axis
Laser beam out
Fully reflective spherical mirror
Laser medium in optical cavity
Absorbing cell for Q-switching
Partially transmitting spherical mirror

FIG. 2. Diagram of the components of a laser device, with three atoms emitting radiation parallel to the axis of propagation.

termed pumping; it is the process of supplying high intensity energy to the atoms or molecules and is accomplished by an electrical discharge or a radiant source such as another laser or an intense light source. The energy conversion process is usually rather inefficient, resulting in the generation of heat. A laser device provides the conditions which optimize the process of population-inversion and stimulated radiation as well as the supply of energy. Because of the generation of heat, most laser devices require a cooling system.

Laser devices have three components, a laser medium, an optical cavity and a pumping source (fig. 2). The name of the laser refers to the type of material used within the optical cavity as the laser medium, which may be a solid, liquid or gas. The laser medium determines the wavelength of the emitted radiation. The most important lasers in medicine today are the CO_2, the Nd–YAG, the Nd–YAG-KTP, argon, krypton and the helium–neon laser. The Nd–YAG–KTP laser is formed by the addition of a potassium titanite phosphate

TABLE I. *Characteristics of lasers used in medicine. CW = Continuous wave*

Laser	Wavelength (nm)	Spectrum	Medium	Pumping	Power (W)
Argon	460–520 (488, 514)	Visible Blue green	Argon ion gas	Elec. discharge	0.0001–5 CW
CO_2	10600	Invisible Infra-red	CO_2 in helium + nitrogen gas	Elec. discharge	0.1–100 CW
Helium–neon	632	Visible Red	Helium–neon gas	Elec. discharge	0.001–0.100 CW
Krypton	400–700 (476, 521, 568, 647)	Visible Blue–red	Krypton gas	Elec. discharge	$\leqslant 10$ CW
Nd–YAG	1064	Invisible Infra-red	Nd–YAG crystal	Krypton or xenon flashtube	CW: 0.5–100 Pulsed: 10^{10} W cm^{-2}
Nd–YAG–KTP	532	Visible Emerald green	Nd–YAG–KTP crystals	Krypton or xenon flashtube	0.5–12 CW
Ruby	694	Visible Red	Ruby rod	Flashtube	$\leqslant 10$ Pulsed
Tunable dye	360–670	Visible Blue-red	Rhodamine in liquid	Argon–krypton laser	CW: $\leqslant 2$ Pulsed: $\leqslant 10$

(KTP) crystal to the Nd–YAG crystal. The KTP crystal doubles the frequency and, thereby, halves the wavelength of the Nd–YAG laser beam. The ruby laser is, medically, of historical value only. The tunable dye laser has more recently been added.

Characteristics of the medically used lasers are given in table I. The optical or resonator cavity provides the controlled environment to which the laser medium is confined. As energy is being supplied to the laser medium by the pumping process, its atoms are raised to their excited states followed by spontaneous emission. Emission occurs in all directions including the long axis of the cavity—the axis of propagation. Usually, two mirrors are positioned, one at each end of the axis of propagation. "Light" emitted along the axis of propagation is reflected back into the optical cavity at an angle depending on the curvature of the reflective surfaces. The reflected radiation may traverse along the long axis to reflect once again off the opposite mirror. Alternatively, the radiation may be absorbed by another atom in the cavity, raising the latter to a higher energy state or, if the atom was already excited, it may result in stimulated emission of the atom. If the latter process is set up along the axis of propagation, multiple reflections between the mirrors (oscillations) will enhance the absorptive and emissive process, building an avalanche effect which increases the intensity of the stimulated emission (along the axis of propagation). The stimulating radiation has thus been amplified. In most lasers, one mirror is fully reflective, while the other is partially transmissive. Various strategies are used to increase the intensity of the stimulated emission, including the intermittent interruption of the reflections. The pattern and distribution of the oscillations in the resonator cavity are influenced by the curvature and position of the mirrors. Ultimately, an equilibrium is reached between radiation leaving the cavity and the rate at which the pumping mechanism can replenish the excited population.

Lasers of the same medium can differ according to their intensity distribution and power output. The latter depends on the particulate size of the active medium and on whether the laser beam is generated by a pulsed or a continuous wave technique. Pulsed lasers can generate a peak energy that is orders of magnitude greater than continuous wave (or CW) lasers. Pulsing can be achieved by Q-switching. The Nd–YAG laser, for example, can be Q-switched by placing a time variable-absorbing cell in the laser cavity. The cell intermittently blocks light reflection at one mirror, but pumping continues so that very high levels of population-inversion are achieved. The cell is suddenly made transparent, allowing stimulated emission to recur with the result that very high power pulses of short duration are generated. Pulses in the gigawatt range and of nano- to picosecond duration are produced. The mode-locked pulsed laser uses a similar absorbing cell strategy. Pulsed laser techniques can also be applied to the CO_2, argon, ruby and dye lasers.

The pulsed laser should not be confused with the terminology for the intermittent use of a laser beam, also referred to as a "pulsed" mode. In the latter case, the duration of a beam output can be set from milliseconds to seconds before firing the beam; the laser will cease output when the time limit is reached if it is not already deactivated by the operator's foot switch. When no time limit is set, the laser is said to operate in the "continuous" mode; the foot switch determines the duration of firing. Typical power outputs for lasers used in medicine are depicted in table I. The aiming beams from the visible helium–neon, argon, krypton, tunable dye and KTP lasers have very low power outputs, the highest being 1–2 mW in the case of the helium–neon laser. Their low outputs are achieved by "splitting" and attenuation of the original beam. The helium–neon laser is used widely in applications requiring precise alignment in medicine and industry; it serves as the aiming guide for the CO_2 and Nd–YAG laser beam.

In addition to the geometrical arrangement of the mirrors around the medium, the intensity distribution within the laser beam depends on focusing lenses through which the beam passes. The shape of the beam determines, in part, the contour of the tissue removed. The intensity distribution in common medical use is the "Gaussian" or transverse electromagnetic mode beam (TEM_{00} mode). The mode of a laser refers to the distribution of energy across the beam—the energy profile. Smaller focal spot sizes and higher power intensities are possible with the TEM_{00} mode beam than with beams of other shapes such as the doughnut of TEM_{01} mode ("Donut") used only experimentally in medicine (fig. 3). The spot size of a laser beam depends also on its wavelength, so that smaller spot sizes are possible with the shorter wavelength of the argon laser as compared

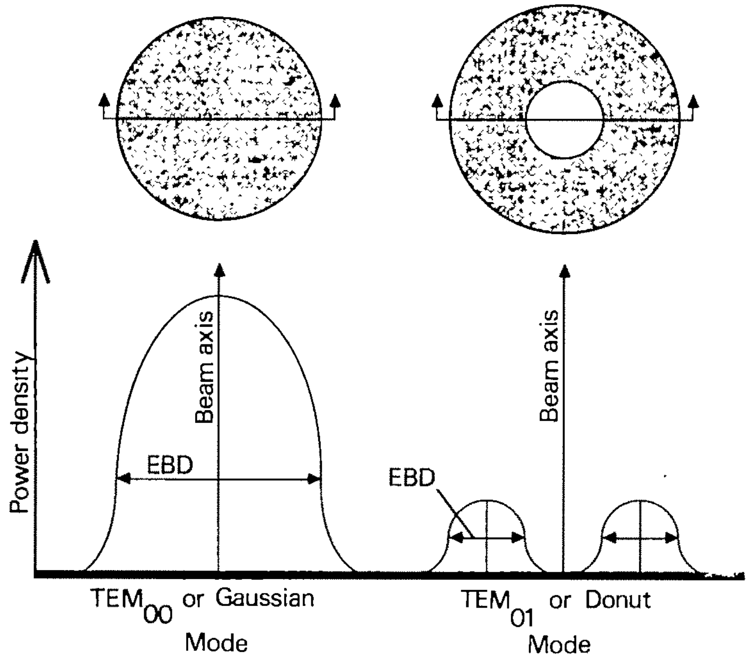

FIG. 3. The intensity distribution of two laser beams. EBD = Effective beam diameter (85% of power under curve).

with the CO_2 laser. It is the laser beam's coherence that enables it to be focused to an extraordinarily small point, thereby giving a very high power density. It is impossible to attain such focusing with non-coherent radiation.

Power density, the power contained in a unit area of beam, is a function of power output and intensity distribution (fig. 3). It is a measure of the concentration of energy of the beam and, in part, determines the area and depth of penetration. Duration of exposure of tissue to the laser is the other important factor in determining depth of penetration. Focusing of the laser beam by suitably placed lenses leads to high power densities. If, for example, a CO_2 laser is unfocused, its beam diameter can approach 1 cm, so that a 10-W laser gives a power density of 10 W cm^{-2}. If the same power is focused on a 1-mm spot size, the power density is approximately 1000 W cm^{-2}. A laser beam which is transmitted through a quartz fibre loses its collimation upon exit from the fibre when it diverges up to 12°.

Interactions of lasers with biological tissues

Electromagnetic radiation falling on tissue is reflected, absorbed or transmitted, or both. The absorbed radiation interacts with the absorbing matter, the nature of the interaction depending on the frequency of the radiation in addition to the composition of the absorbant. Gamma radiation and x-rays travel a greater distance in tissues than lasers and cause molecular excitation and ionization. Most medical lasers utilize light of wavelengths in the visible and the infra-red (invisible) portion of the spectrum; their absorption leads predominantly to heating, not to ionization. Depending on the rate of energy delivery or flux, heating, caused by a laser beam with a low flux, initially causes coagulation of proteins but, if further energy is absorbed, the intracellular water expands, vaporizes and the cell ruptures. The flux of a well-focused CO_2 laser beam is so high that almost immediate vaporization of cells takes place and the dehydrated residues break down in the laser beam. Carbonization of proteins and other cellular components occurs at the edge of this process. The flux of the Nd–YAG laser beam causes predominantly coagulation of proteinaceous elements of the tissues and carbonization occurs in an area larger than that affected by the CO_2 laser beam. Because of differences in power density, energy flux and depth of penetration of the various laser beams, their effects on tissues differ greatly.

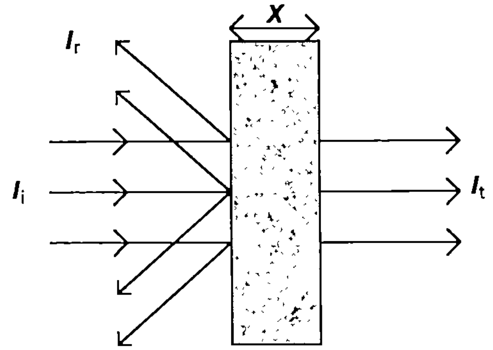

FIG. 4. Reflection, transmission and absorption of the laser beam. The absorbed component is $I_a = I_0 - I_t$, where $I_0 = I_1 - I_r$ and the transmitted beam $I_t = I_0 \times 10^{-\acute{a}X}$, where $\acute{a}$ = absorption coefficient and X = thickness of material. (Reproduced with permission from: Polanyi TG. Laser Physics. *Otolaryngologic Clinics of North America* 1983; 16: 753.

The depth of penetration, and the width of the area affected by a laser beam, depends on many factors. Consider a beam of intensity I_1 impinging on a thin slab of thickness X (fig. 4). I_r represents the reflected portion and I_t the transmitted portion of the beam. The absorbed component, I_a, is $I_0 - I_t$, where I_0 equals $I_1 - I_r$, the net beam intensity transmitted past the incident interface. The intensity of the transmitted beam, I_t, is related to the net beam intensity, I_0, by Beer's law, $I_t = I_0 \times 10^{-\acute{a}X}$, where X is the thickness of the material and $\acute{a}$ is the absorption coefficient. The latter depends on the wavelength and on the physical and chemical composition of the absorbing material. The greater the value of $\acute{a}$, the lesser the value of I_t. When X equals $1/\acute{a}$, then I_t equals $I_0 \times 10^{-1}$, or 0.1 I_0; that is, 10% of the incident beam I_1 is transmitted in thickness X of the material. In other words, 90% of the incident beam is absorbed in this distance X, which is termed the extinction length (EL). In three EL, absorption is virtually complete, the bulk of the radiation being present to a depth of one extinction length. Part of the laser beam transmitted past the incident interface is scattered by the tissues. Scattering is strong if absorption is low and if the material is very inhomogeneous. The overall effect is to reduce EL. The effective cross-sectional area of the incident beam is increased by scattering and the critical volume (CV), the volume in which 90% of the interactions with the material take place, is enlarged.

The application of lasers is influenced strongly by the aforementioned physical properties and they are applied to a wide range of pathology (table II). Correct selection of the type of laser most efficiently absorbed by the target tissue reduces the chance of damage to adjacent tissues. Brief intermittent exposures allow controlled destruction and dissipation of heat in addition to assessment of the treatment. The CO_2 laser beam is absorbed strongly by water, blood and biological tissues. The EL is approximately 0.03 mm in most tissues and water, and it has thereby the shallowest penetration of the medical lasers. Reflection and scattering are negligible. Most of the energy is used for vaporization and little is dissipated as heat at the margins of the CV where only small amounts of coagulated and carbonized material collect. Oedema formation is minimal. The limited penetrance with minimal surrounding damage makes the CO_2 laser especially suited as a "cutting" tool. At lower power settings, coagulation and fair to good haemostasis are possible of vessels up to 0.5 mm in diameter. The overall effects can be summed up as "what you see is what you get", unlike the effects resulting from the Nd–YAG laser beam. The CO_2 laser beam is not transmissible through standard quartz fibres, but is transmissible through others such as the near-infra-red silica-based fibres and metal halides (e.g. thallium bromoiodide, Matsushita Co.) [27, 66].

The Nd–YAG laser beam, on the other hand, is absorbed weakly by pure water, in which it has an EL of 60 mm. Its absorption is greatly increased by pigmentation and scattering in tissue is strong, with back scattering of 20–40%. The EL for Nd–YAG in soft tissue is 2 ± 1 mm, which is 30-100 times longer than the EL for a CO_2 laser; it provides the deepest penetration among the medical lasers. An Nd–YAG laser beam diameter expands approximately three times when traversing a 2-mm thickness of bladder mucosa, increasing the cross-sectional area nine-fold. Thus, the CV of the Nd–YAG laser beam is 300–900 times larger than the CV of the CO_2 laser. Because greater volumes of tissue are involved, the devitalization process is much slower with the Nd–YAG laser and the dissipation of heat leads to a more diffuse thermal effect which also results in more oedema formation; it can be called a coagulator of tissues.

The area affected by the Nd–YAG laser beam can be likened to the shape of an iceberg; only the tip of the affected area is visible on the surface of the target tissue. Because of the deeply seated

TABLE II. *Surgical applications of lasers commonly used in medicine*

Laser	Medical field	Applications
CO_2	Dermatology and plastics	Excision of burns, haemangiomas, keratosis, telangectasia, spider nevi, melanomas, basal and squamous cell carcinomas, subcutaneous mastectomies, mammoplasties
	General surgery	Liver and spleen resections, breast lumpectomy, mastectomy, gastrectomy, colostomy, polypectomy
	Gynaecology	Cervical, vaginal and vulval neoplasms, tuboplasties, condylomata excision, endometriosis
	Neurosurgery	(Vascular) tumours
	Otolaryngology	All tumorous and obstructive processes of the naso–oro–laryngo–tracheal area (polyps, cysts, haemangiomas, lymphoma, papillomas, carcinomas, choanal atresia, etc.)
Nd–YAG	General surgery	Liver and spleen resections, polypectomy, mastectomy
	Gynaecology	(See CO_2 applications and menorrhagia)
	Neurosurgery	(Vascular) tumours
	Gastroenterology	Bleeding gastric erosions, carcinomas, polyps, vascular lesions (e.g. Osler–Weber–Rendu, etc.)
	Urology	Bladder tumours
	Otolaryngology	Tracheobronchial tumours
	Pulmonology	Tracheobronchial tumours
	Ophthalmology	Vitreous and posterior capsular surgery (Pulsed mode)
Nd–YAG–KTP	Neurosurgery	(Vascular) tumours
	Otolaryngology	Tympanoplasty, myringotomy, stapedectomy
Argon	Ophthalmology	Glaucoma, retinal surgery (detachments, many retinopathies such as in diabetes)
	Dermatology and plastics	Port wine stains, haemangiomas, tattoo removal
	Neurosurgery	(Vascular) tumours
	Otolaryngology	Tympanoplasty, myringotomy, stapedectomy
	Gastroenterology	(See Nd–YAG applications)
Krypton	Ophthalmology	(See argon applications)
Tunable dye	Ophthalmology	(See argon applications)
	Oncology	HPD tumour therapy

coagulation and oedema formation, other effects, including complications such as haemorrhage or obstruction, may be delayed by 1 or 2 days. When a high flux is used the centre of the "iceberg" may undergo vaporization, with rapid expansion of the tissues, resulting in a limited explosion of the overlying tissue—the "popcorn" effect. Its absorption by pigments makes it suitable for the control of bleeding gastric erosions, vascular lesions and polyps. Haemostasis of vessels up to 5 mm can be achieved. The short wavelength of this laser allows the beam to be transmitted by fibreoptic bundles to otherwise inaccessible parts of the body. Various shapes of sapphire tips can be mounted on the end of the fibre, resulting in the concentration of the Nd–YAG laser beam at the tip with considerable divergence just beyond the tip. This technique allows the sapphire tip to be brought into contact with the target tissue where coagulation or slow cutting can be achieved; the sapphire-tipped fibre can be advanced in endoscopes as well as in hand-held tools. The Q-switched (in addition to the mode-locked) Nd–YAG laser, one of the few medical applications of a pulsed laser, is used for posterior capsulotomy after cataract removal and other ophthalmic procedures such as iridotomy and vitreolysis [3, 65]. Very short (nanosecond), very high power density bursts can be delivered to the opacified posterior capsule, creating a "window" without injury to the retina. The very short, high power density pulses shatter the tissue by optical breakdown, tearing the molecules and cells apart with a shock wave effect; the thermal effects are of relatively little importance in this application (2, 46, 93).

The argon laser exhibits considerable variability in its absorptive, scattering and reflective properties. It is absorbed strongly by haemoglobin and pigmented tissue, transmitted by homogeneous, watery tissue and scattered by non-pigmented, inhomogeneous tissues. The EL in water is 300 mm. The argon laser is ideally suited for retinal photocoagulation and other ophthalmological procedures. Absorption by blood enables excellent haemostasis. It can be transmitted by way of optical fibres so that it can be used for the endoscopic treatment of gastrointestinal bleeding. The haemostatic properties are inferior to those of the Nd–YAG laser because the greater CV of the latter allows control of bleeding from vessels several millimetres in diameter. The argon laser's short wavelength makes very small spot sizes possible, typically 20 times smaller than the spot size of the CO_2 laser beam and, its beam being in the visible part of the spectrum, misalignment between the laser beam and a separate aiming beam is obviated.

The Nd–YAG–KTP laser beam possesses many of the characteristics of the argon laser with respect to its variability in its absorptive, scattering and reflective properties. It, too, is transmissible by way of quartz fibreoptic bundles. Its absorption by blood is high, by water low and its tissue absorption is less than the CO_2 laser beam but stronger than the Nd–YAG. The 647-nm krypton laser is in the red part of the spectrum; it passes easily through watery, homogeneous tissues as well as blood and is strongly absorbed by certain pigments in the retina. The tunable dye lasers generate frequencies in the range of the argon and krypton laser and are just reaching ophthalmological practice.

The ruby laser has been largely superseded by the argon and krypton lasers, but was used previously in ophthalmic surgery. The EL in water is 300 m, its scatter is high and it is transmissible by quartz fibre. It is absorbed strongly by melanin, but not by haemoglobin, and has a limited coagulation capability. It was used to repair retinal tears, the purpose being to produce an adhesive chorioretinitis. However, its limited haemostatic properties allowed small haemorrhages to occur.

Safety considerations for laser surgery

The lasers used in medical practice today do not cause ionization, are not carcinogenic and do not form a special hazard to pregnant women. It is imperative, however, that the laser beam be in an inactive or standby mode at all times except when the beam is aimed at an appropriate target. The laser beam is reflected by shiny, flat or concave surfaces deflecting it in unintended directions. The beam's reflections and backscatter (Nd–YAG) can also cause injury. Reflection can be reduced by providing matt finished, convex surfaces for operating room equipment. A matt finish can be obtained by sandblasting or shot-peening, creating microscopic pits from which the beam is deflected in all directions. The microscopic pits and the convex surfaces diverge and defocus the laser beam, thereby reducing its power density over a short distance.

Trauma to the patient's normal tissues can occur as extensions of the laser treatment with immediate or delayed sequelae including perforations, haemorrhage, pneumomediastinum and pneumothorax. These conditions may require emergency treatment for which the anaesthetic and surgical team need to be prepared. In addition to healthy tissues adjacent to the site of treatment in the patient, the eyes and epidermis of the patient and operating room personnel form accidental targets for a reflected beam.

The eye is the tissue most susceptible to laser injury. The CO_2 laser beam, with its short EL, can lead to corneal damage [43]. Light from the argon, krypton, Nd–YAG–KTP, and ruby lasers passes through the cornea and lens but is absorbed strongly by pigmentation. It may cause retinal damage. The Nd–YAG laser light is also well absorbed by the retina. In order to prevent eye damage, operating room personnel should wear protective eyeglasses which absorb the radiation of the wavelength of the laser in use. Their main purpose is to protect the eyes from accidental reflections and scatter of the beam; *appropriate glasses do not protect the eyes against a direct hit from a focused beam at close range*. Glass, transparent plastic or quartz glasses *with side protectors* are worn when the CO_2 laser is in use; contact lenses do not afford sufficient protection. The Nd–YAG laser light is absorbed by glasses which block the 1064-nm light. It should be noted that these glasses do not protect the eyes from the Nd–YAG–KTP laser light, which requires orange–red lenses to be worn. During use of the argon laser, orange–yellow lenses protect the eyes against the short wavelength of the green–blue spectrum; glasses which filter out the appropriate wavelength should be worn for the krypton beam. The "tunnel vision" and the reduced luminous transmission inevitably produced by such eyeware limit observation of the patient and the monitoring equipment, but are minimized by the use of specially designed glasses with transparent side protectors and nearly "clear" lenses.

The detection of cyanosis is more difficult when coloured lenses are used, and we recommend continuous haemoglobin saturation monitoring (e.g. pulse oximetry). The attenuated aiming beams of the helium-neon, argon, krypton, tunable dye, and Nd–YAG–KTP lasers have very low power outputs and can be viewed indirectly or from the side with the unprotected eye; however, one should not look into these aiming beams directly or "on-end", unless they are specifically attenuated to be used intra-ocularly as in ophthalmic applications (the helium-neon, argon, krypton and tunable dye aiming beams).

In order to prevent injury to the patient's eyes, these are covered with moist pads held on with canvas tape. Plastic or paper tapes may flare up and should be avoided. Wet cloth towels cover the surrounding surgical field. In neonates and infants, in particular during long procedures, care is taken to minimize direct skin contact as it leads to patient hypothermia. Paper or plastic-coated paper towels are similarly avoided, because they wet poorly and may ignite. Heating of metal instruments may lead to burns, especially in the anaesthetized patient. During the use of lasers for colonic surgery and laparoscopy, a non-combustible gas, for example CO_2, is used for insufflation. Gases from the lower gastrointestinal tract should be evacuated, because they may contain methane. Accidental burns from laser-ignited combustion of flammable materials may occur from elastomeric tracheal tubes, flexible endoscopes and other combustible material around the surgical field. Tracheal tube ignition and explosions, and unintended facial burns, are the most common complications of the use of the CO_2 laser [26]. Claims about toxic, carcinogenic and infective properties of smoke, generated by the CO_2 laser beam's interactions with the tissues, have not been substantiated by either *in vitro* or *in vivo* studies [90]. Smoke can be suctioned away to improve visibility.

Complications may arise owing to the special equipment and instrumentation required. The CO_2 laser comprises the laser head, attached by an articulated arm to the operating microscope, and a control console connected by a single multipurpose tether. In addition to the invisible CO_2 laser beam, the head carries the helium–neon laser beam which serves as the aiming beam. The microscope is brought into alignment with the larynx and the micromanipulator moves a mirror in the laser head, aiming the helium–neon laser beam at the target. Misalignment of the helium–neon aiming beam with the CO_2 and the Nd–YAG laser beam or poor focusing of a laser beam can lead to trauma to normal tissue. The Nd–YAG laser beam and its helium–neon aiming beam are carried coaxially by a flexible quartz fibre from the laser console to the endoscope; the fibre has a Teflon sheet through which a cooling gas (e.g. nitrogen, helium, helox, air) is pumped, flushing the tip. The total fibre is advanced in a channel of either a rigid or a flexible fibreoptic bronchoscope. The tip of the fibre should protrude beyond the bronchoscope port at all times during its operation, under "direct" vision (via appropriate optics) of the operator. The fibre and the flexible bronchoscope are advanced well beyond the flammable tracheal tube. Firing of the Nd–YAG laser inside a flexible fibreoptic bronchoscope or an elastomeric tracheal tube can cause ignition. The metal bronchoscope excludes this possibility. To avoid combustion during the use of the Nd–YAG laser, it is important to keep the fibre tip clean and flushed with cooling gas. If the fibre tip is allowed to collect debris, it will melt and flare up. Most medically used lasers are high voltage, high current electrical devices with protective circuitry which shuts the laser down when malfunction occurs. The electrical hazards should be kept in mind; a laser should not be operated when the operating room floor is wet [25]. Operators of the laser and their assistants are preferably trained and certified within a given hospital [1]. Warning notices that a laser is in use are posted outside the operating room. The flow of traffic in and out of the operating room is minimized; the windows are blocked. Anaesthesia should not begin until the equipment is set up and checked, otherwise it may be prolonged unnecessarily.

Clinical considerations of airway surgery

The CO_2 laser is used predominantly in the upper airway to excise a variety of benign and malignant lesions (table II). It provides good haemostasis of small blood vessels, minimal postoperative oedema and good healing with little scar formation, making it invaluable in the small paediatric airway [97]. Rigid bronchoscopy permits treatment of tracheobronchial lesions with the CO_2 laser, while both the rigid and flexible bronchoscope permit their treatment with the

Nd–YAG laser [18, 91]. The Nd–YAG laser can be applied more efficiently in the distal tracheobronchial tree through a flexible fibre system with better optical control and secure haemostasis, especially when haemorrhage occurs from larger vessels (0.5–5 mm). It is particularly suited for palliative treatment of obstructive tracheobronchial malignancies [19, 76, 79]. The need to share access to the airway requires close cooperation and understanding of surgeons and anaesthetists [55].

Problems of airway management during laser surgery may arise from the underlying pathology and instrumentation. Specific anaesthetic techniques, suitable for each patient with airway pathology in need of surgery, do not need to be outlined here. However, a few points are worth emphasizing. The pathology for which the patient seeks treatment has often resulted in a marginal airway. Ventilatory obstruction with copious secretion and hypoxaemia may have led to respiratory and cardiovascular compromise or may have exacerbated co-existing disease. Careful preoperative assessment, including roentgenographic evaluation (chest x-ray, computed tomography), is essential. A detailed explanation of the proposed anaesthetic technique and surgical plan may help to produce a calm, relaxed patient. It is prudent not to give sedative or opioid agents to patients with a compromised airway, except after careful deliberation.

Anticholinergic drugs such as atropine, hyoscine and glycopyrrolate, may be useful to dry secretions and may reduce the vagal effects of laryngoscopy. Intra-operative monitoring includes electrocardiogram arterial pressure and breath sounds using a precordial stethoscope. Percutaneous pulse oximetry offers reliable, fast and continuous evaluation of haemoglobin saturation [5, 104]. Direct arterial pressure monitoring and blood-gas analysis may be helpful in some patients.

Securing a patent airway may be the first step towards the patient's treatment. Satisfactory ventilation may not be established, however, until obstructions or sites of haemorrhage have been treated with the laser. Loss of muscle tone during induction of general anaesthesia may render a partial airway obstruction complete; an inhalation induction or intubation under local anaesthesia may be required. Full muscle relaxation offers optimal conditions for re-intubation should accidental extubation or tracheal tube ignition occur, provided that reintubation is easily accomplished. A deep level of anaesthesia can minimize the cardiovascular responses to instrumentation of the airway.

The larynx is exposed with a Jako or Dedo laryngoscope which is placed on a suspension apparatus. Patients in whom the larynogoscopy is difficult may be prone to injury from this procedure. Tooth damage or temporomandibular joint dislocation can occur during the exposure. A preoperative history of syncope or dizzy spells during neck movement may indicate the presence of vascular insufficiency. Similar concerns regarding positioning apply to the use of the Nd–YAG laser via the rigid bronchoscope.

Lasers, ventilation and tracheal tubes

Polyvinyl chloride and rubber tubes. When a CO_2 laser beam strikes a tracheal tube, ignition may occur [82]. The likelihood of such an event is determined by the type of tube (combustible material), the wattage of the laser beam, the duration of exposure of the tube to the beam, and a gas mixture supportive of combustion. PVC tubes are more ignitable than red rubber tubes when exposed to CO_2 laser beams of 15 and 30 W intensity for periods of 0.015–0.5 s in an atmosphere of 25 or 60 % oxygen in nitrous oxide [61]. No penetration of either tube occurred in an atmosphere of 25 % oxygen in nitrous oxide and a beam intensity of 15 W. Even at exposures of 0.5 s only superficial burns of the red rubber tubes resulted. However, all the PVC tubes either ignited or were penetrated during exposures of 0.5 s by a beam of 30 W intensity, whereas only one out of 10 red rubber tubes sustained damage. Oxygen concentration had a marked effect, with PVC tubes burning vigorously in 60 % oxygen in nitrous oxide and the burned area being more localized when 25 % oxygen in nitrous oxide was used. Red rubber tubes produced less smoke, and aluminium tape wrapping significantly retarded the ignition of both types of tube.

In another study, PVC and red rubber tubes were irradiated with beam intensities of 5–20 W for durations of up to 1 s in 50 % or 100 % oxygen; the diluent gases were not specified. The greater ignitability of PVC tubes was again confirmed [48]. However, the advantage of red rubber tubes was not demonstrated in a third study in which evidence of combustion was detected in an atmosphere of 30 % oxygen in air at intensities of 15 W or greater, for exposures of more than 0.05 s [92]. Although the evidence is conflicting, red rubber tubes are generally regarded as safer than PVC tubes. The authors' recommendations for "safe" gas mixtures include 20–25% oxygen without specification of diluent gases [61], 20–30% oxygen in nitrogen [92] or no critical oxygen limit provided that red rubber tracheal tubes wrapped in aluminium foil are used and direct hits are avoided [48]. However, all elastomeric tracheal tubes are combustible to a variable degree.

Tracheal tube protection. Tracheal tubes can be protected by wrapping with reflective aluminium or other metallic tape. In view of the greater combustibility of PVC tubes, it is preferable to use the less flammable ones such as the red rubber tubes. Wrapping starts at the superior border of the cuff, each turn smoothly overlapping the previous one by at least one ¼–⅓ width. This allows the tube to be flexed without exposing the underlying tube and without breaking or kinking the tape. The cuff should be protected with damp cottonoids and can be filled with saline or lignocaine [41]. Disadvantages of this wrapping method are that it reduces tube flexibility, increases the external diameter, can produce rough serrated surfaces which may be traumatic and may be more difficult for intubation; the foil wrapping may become detached. These factors limit their usefulness in the small paediatric airway. Depending on the wattage and exposure time of the laser beam, in addition to the thickness and coating (Milar, glue) of the aluminium, foil, reflection, pitting and penetration of the aluminium foil are still possible. However, the processes are much retarded. Copper foil is also used for wrapping; it is less reflective than aluminium foil, has a greater heat capacitance and conductivity and may lead earlier to burn injury of adjacent tissues. Muslin wrapped tubes may ignite if the muslin is allowed to dry out. It adds bulk and the technique offers little advantage over wrapping with aluminium foil [85]. Metallic foil wrapping of elastomeric tracheal tubes does not offer protection from damage caused by an impinging Nd–YAG laser [28].

Silicone tracheal tubes. The safety of metal-loaded (aluminium oxide) silicone tracheal tubes, such as the Xomed Laser-shield, has not been fully evaluated. A preliminary communication reported that penetration of the silicone tube was not possible with pulses of 5–25 W for a duration of 0.1–1.0 s in an atmosphere of 30–100% oxygen in nitrogen or nitrous oxide [31]. These preliminary data suggest significantly different characteristics compared with other silicone and PVC based tubes. Silicone tubes were associated with the least amount of gross anatomical and histological damage compared with PVC or red rubber tracheal tubes [59]. A 30-W CO_2 laser beam impacted on the tubes until an intraluminal, blowtorch-like airway fire existed. Thirty percent oxygen in 70% nitrous oxide and halothane formed the anaesthetic gas mixture in this canine model.

In a recent study, the relative flammability, rather than the ignitability, of PVC, silicone and red rubber tubes were compared in oxygen–nitrous oxide–nitrogen atmospheres using a standard ignition source [100]. Ignition refers to the amount of energy needed to ignite a fuel in a given atmosphere, whereas flammability of a fuel is its ability to sustain a flame in a given atmosphere. In a given gas mixture, red rubber tubes were the most flammable, followed by silicone tubes in turn followed by PVC tracheal tubes, which were the least flammable. PVC tracheal tubes sustained a flame when a minimum of 26% oxygen in nitrogen was present.

The Milhaud and Rusch Injecto-Flex silicone rubber tubes are other examples of attempts to reduce fire-hazards. The Milhaud tracheal tube utilizes nitrogen as a "flushing" gas above the cords to cool the tube and to reduce the risk of explosion [49]. A silicone rubber shield loaded with aluminium powder is positioned just proximal to the cuff, preventing radiation reaching the balloon and distal structures. The Carden tube is a short (5-cm), cuffed, silicone rubber tube which is placed in the trachea [11, 12]. Two small rubber catheters pass through the vocal cords, one for "jetting" gas and one for inflation of the latex cuff. This tube is used also for microlaryngeal laser surgery, in which case the pilot lines are covered with wet cottonoids. All elastomeric tracheal tubes are damaged by the Nd–YAG laser [28].

Trans-tracheal catheters and needles. In an attempt to increase visibility and to reduce exposure of combustible material to the laser beam, plastic or silicone rubber catheters and small diameter metal tubes (long needles or small tubes) have been inserted into the trachea [34, 36, 58, 64, 67, 69, 83]. Ventilation is accomplished by "jetting" a gas mixture, controlled manually or mechanically, down the trachea. These forms of ventilation do not predominantly, if at all, depend on the Venturi principle. The catheters provide combustible material and, when severed, parts may be lost in the tracheobronchial tree. Mucosal tears may be generated at the tip of the metal ones. Pressures, generated during the "jetting", are directly transmitted to the lung and are more likely to result in barotrauma than other techniques. The amount of gas delivered to the lungs is not limited by inspiratory obstructions, since the catheters usually bypass these points. Exhalation becomes a limiting factor. In order to avoid barotrauma care must be taken to ensure a patent exhalation route. Patients with pulmonary disease, especially those with air trapping, are susceptible to barotrauma with these techniques. This difference between inhalation and exhalation does not exist in Venturi jet ventilation through an operating laryngoscope.

Metal tubes. The only non-combustible tubes are made of metal. The Norton tube is a matt-surfaced, convex, reflective, segmented metal tracheal tube; its coils are not airtight, so that gas flow through the coils aids cooling of the metal [57]. A standard anaesthetic breathing system with a reservoir bag is connected to the tube; the fresh gas flow is increased to compensate for the gas escaping through the coil and around the tube. If sufficient ventilation cannot be maintained a latex cuff, which may be inflated with a liquid (water) and needs to be covered with wet cottonoids, can be added to the tube. However, these manoeuvres provide combustible material. Alternatively, a Woo–Pilling Venturi jet tracheal tube coupler with a 12-gauge needle is clamped onto the proximal end of the metal tracheal tube and gaseous exchange is established by Venturi jet ventilation [102]. The Norton tube needs an introducer during intubation because of its flexibility. The smallest, 4.4-mm i.d. Norton tube has an external diameter of 6.5–8.0 mm. The Porch tube is an airtight flexible metal tube (3 mm i.d., 7 mm o.d.) connected directly to a high pressure gas source via a Luer–Lok fitting [34]. Its behaviour, in terms of gas dynamics, is that of a large metal needle below the vocal cords rather than that of a tracheal tube. It is not commercially available. Both metal tubes are relatively large and do not give an unobstructed view of the larynx; their use in patients with a narrow airway, as in small children, is precluded.

Gases and vapours. Some authors recommend the substitution of nitrous oxide, which supports combustion, by inert gases such as nitrogen or helium, thereby delaying ignition of combustible material. Evaluating PVC tracheal tubes, Pashayan and Gravenstein demonstrated that oxygen in helium retards ignition, but only if the oxygen concentration is less than 40%, the laser beam intensity is less than 10 W and continuous exposure is less than 10 s [60]. All PVC tubes could be penetrated easily at the lowest power settings, but they did not ignite under these conditions. The mean time to ignition of PVC tubes is shorter when 2% halothane is added and when the laser beam is directed at the barium sulphate indicator strip. It is suggested that nitrous oxide and halothane be avoided because of the formation of toxic products at high temperatures [61]; however, these concerns are of little clinical relevance during laser surgery [6, 42]. The anaesthetic gases and vapours (halothane, enflurane and isoflurane) are not themselves combustible under medical conditions.

Venturi ventilation. Venturi jet ventilation through an operating laryngoscope provides an unobstructed view, avoidance of combustible material, clearing of smoke and is usable for small openings in the smallest neonate without the need to restrict oxygen content. The intermittent use of Venturi jet ventilation permits the taking of biopsies, the removal of tumours or debris and the lasing of vocal cords in the absence of vibrations.

The application of the Bernoulli theorem and the Venturi principle to gases is outlined diagrammatically in figure 4 [52]. Gas under high pressure (the jet) exits from a needle or nozzle placed within the lumen of a specially shaped open-ended tube. In addition to the propulsive effect of the jet on the resting gas column, the pressure around the needle and behind the jet exit point becomes lower with respect to the pressure in the mainstream gas flow, with the result that ambient gas is entrained through the open proximal end of the tube (the entrainment orifice). The shape of laryngoscopes and bronchoscopes is not optimized for an optimal Venturi effect to take place. Other important factors are the site and size of the entrainment orifice, the force of the jet, the placement of the jet within the outer tube and the dimensions of the outer tube. The force of the jet leaving the needle depends on the driving pressure, the needle diameter, length, angulations and restrictions. The density and viscosity of the gas mixtures determine in part the type and volume of gas flow. The volume of gas leaving the outer tube may be 20 times that of the jet, and it is at a lower

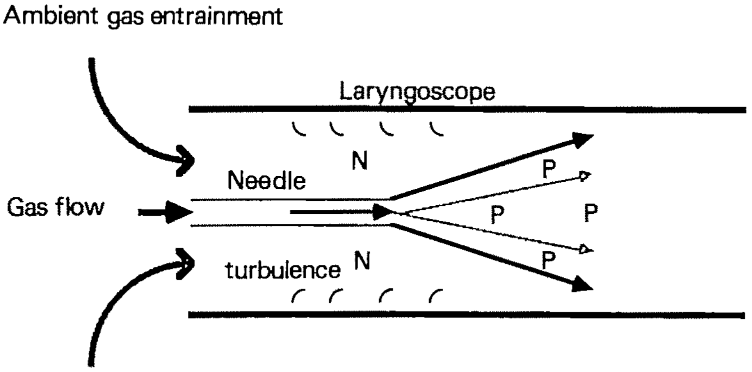

FIG. 5. Simplified diagram of the application to gases of the Venturi effect and Bernouilli principle. P = High pressure area; N = relative negative pressure (compared with P).

pressure. The best position of the needle tip for maximum safety and efficient gas exchange is at the middle one-third of the laryngoscope [101]. A stainless steel needle is inserted coaxially into the lumen of the operating laryngoscope, which is in alignment with the trachea. A screw clamp holds the stainless steel needle in place. The needle is angled just proximal to the clamp, and is connected by "pop-off", non-locking fittings to light weight, pliable, low pressure tubing, a manually operated, all-or-none trigger valve and a pressure gauge with a reducing valve connected to a high pressure (400-kPa) gas source (fig. 5). The trigger valve releases a stream of gas to flow down the laryngoscope into the trachea. Although the trigger can be operated automatically, manual operation is preferable because it enables greater control of the airway pressure and ventilation can be co-ordinated with the needs of the surgeon. The "needle-on-clamp" construction (fig. 6) is applicable to all operating laryngoscopes without modification, while all light and suction ports remain available. The light channel of an operating laryngoscope can also be used satisfactorily for delivery of the jet [73].

Peak inflation pressures and tidal volume depend on the driving pressure, needle diameter and length, internal diameter of the operating laryngoscope and compliance of the ventilatory system. Regulator pressures of 150–300 kPa in adults and 30–150 kPa in children are recommended, with the use of a 12–14 gauge needle for patients heavier than 100 kg, a 14–16 gauge needle for patients of 50–100 kg and a 16–18 gauge needle for those weighing less than 50 kg [101]. Before its use, the gas jet issuing from the needle is tested, at a distance of 1 cm, on the skin of the forearm, where it should generate a slight depression. Jet ventilation should start at low driving pressure settings and the driving pressure is increased gradually according to chest expansion, "breath" and transmitted sounds and other clinical criteria. The lowest regulator pressure which gives chest expansion is utilized. Sufficient time for exhalation is provided. The pressures generated by the gas stream leaving the operating laryngoscope are not the same and much lower than the driving pressures supplied to the needle [39, 71, 73]. Ventilation takes place with either oxygen or an oxygen and nitrous oxide mixture, although it is realized that the gas mixture delivered to the patient is altered by the entrainment of ambient gas [73]. Arterial blood-gas measurements have demonstrated the adequacy of gaseous exchange [54, 56, 73]. There is usually a tendency to hyperventilate, and inadequate oxygenation is rarely a problem. Full muscle relaxation provides a maximally compliant chest with minimal cord movement, while the incidence of laryngospasm and coughing are reduced.

Suction devices for evacuation of smoke can interfere with Venturi jet ventilation [50]. Complications of Venturi ventilation include barotrauma of the respiratory tract, but this is a rare complication. Venturi ventilation through a laryngoscope is also an option in the patient with a tracheostomy. The stoma can be covered with a sterile wet dressing to which gentle pressure is applied to prevent a gas leak. Mucosal drying may accompany the use of Venturi ventilation; it is a possible advantage when excessive secretions reduce the effectiveness of the CO_2 laser.

During Venturi jet ventilation, general anaesthesia is usually maintained by intermittent or

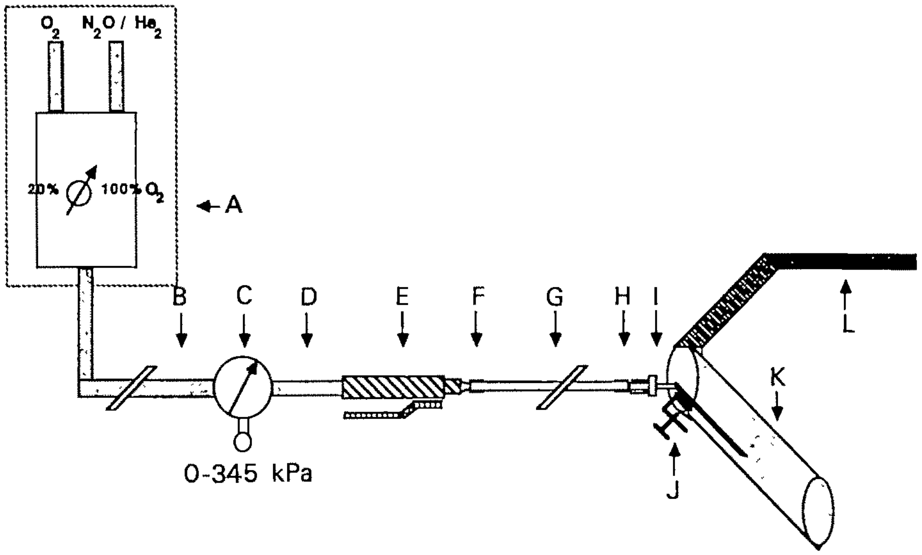

FIG. 6. The Venturi ventilation apparatus with injector needle-on-clamp. A = high pressure gas source with optional oxygen–nitrous oxide or helium blender; B = high pressure tubing; C = reducing valve and pressure gauge; D = short piece of high pressure tubing; E = manual, all-or-none, trigger valve; F = tapered metal connector of the "pop-off" type; G = low pressure plastic tubing; H = optional Luer–Lok fitting on tapered metal connector of the "pop-off" type; I = an adapted, curved stainless steel needle, 12–18 gauge; J = screw clamp to fit on the edge of the operating laryngoscope; K = a schematic outline of the operating laryngoscope; L = the laryngoscope handle which fits the suspension apparatus. Fitting F and H should be able to "pop-off" when high pressure is inadvertently transmitted to the low pressure tubing (when C, E or both are failing) or when an obstruction occurs distally.

continuous i.v. infusions with anaesthetic agents including barbiturates (methohexitone, thiopentone), short acting opioids (alfentanil, sufentanil, fentanyl), benzodiazepines (midazolam, diazepam), ketamine or droperidol. Inhalation agents can be used if a separate entrainment system provides the desired gas mixtures [39].

Bronchoscopy. Laser therapy of the tracheobronchial tree has been undertaken with the CO_2 and Nd–YAG laser beams. The CO_2 laser beam is applied via the rigid ventilating bronchoscope during general anaesthesia [78, 79, 89]. During CO_2 lasing, the working channel of the ventilating bronchoscope is not obstructed by instruments, but ventilation can be impeded by the position of the bronchoscope in the tracheobronchial tree and by obstructive pathology. When telescopes, forceps or other instruments are used, partial obstruction of the working channel of the ventilating bronchoscope occurs; when its proximal end is open, anaesthetic gas can escape to the atmosphere via the proximal end. Inhalation anaesthesia with halothane or enflurane in 100% oxygen or in an oxygen–nitrous oxide mixture delivered by a conventional anaesthetic circuit with an anaesthetic reservoir bag via the side arm (bag ventilation) results in adequate ventilation. The use of 100% oxygen leads occasionally to incandescence of dried carbonized particles, but without sequelae [78, 89].

The Nd–YAG laser has taken over in importance from the CO_2 laser, because of better haemostatic properties, transmission through flexible quartz monofilaments, easier application and the ability to use better optics [8, 18, 79, 91]. It is applied via the flexible or rigid bronchoscope during local or general anaesthesia. Although the use of the flexible bronchoscope for YAG laser application has its proponents, the emphasis of tracheobronchial YAG therapy has shifted to its application via the rigid bronchoscope during general anaesthesia [8, 19]. The rigid bronchoscope allows better access to tracheobronchial pathology with forceps, balloons, dilators, suction catheters, etc. It facilitates treatment of bleeding, allows suction of large volumes of blood, pus, secretions or irrigation fluid, and the easier retrieval of tumour and debris. The rigid bronchoscope also permits palpation and delineation of the tumour and the tracheobronchial wall; when obstructive pathology threatens airway patency, it can provide and maintain a patent airway by advancing the bronchoscope beyond the tumour mass. Rigid bronchoscopy is particularly well suited for large, obstructive lesions in the trachea and mainstem bronchi, whereas the flexible endoscope is useful for smaller and more distal pathology which may not be reached with the rigid bronchoscope [76, 79].

The flexible fibreoptic bronchoscope for YAG laser application (o.d. ⩾ 6 mm) can be passed nasotracheally in the awake patient, via a tracheal tube (i.d. ⩾ 8 mm) with swivel or membrane connector during general anaesthesia or via the rigid bronchoscope during either local or general anaesthesia [9, 17, 44, 68]. Flexible fibreoptic bronchoscopy is well suited for the preoperative assessment of the pulmonary pathology; local anaesthesia for the nasotracheal passage of the fibrescope is accomplished easily by the use of lignocaine applied through a nasal spray and an ultrasonic nebulizer. Flexible bronchoscopy for the YAG application under local anaesthesia may appear attractive since it avoids general anaesthesia. It may be reserved for selected patients. However, coughing and restlessness during local anaesthesia, especially in the hypoxaemic patient, provides less suitable operative conditions and general anaesthesia provides better airway control [19]. Hypoxaemia, haemorrhage and perforation are the main complications of Nd–YAG laser therapy of the tracheobronchial tree [75]. Maintenance of a patent airway with adequate ventilation and oxygenation, in addition to control of haemorrhage, are the key to successful therapy. Short (⩽ 1-s), low power (⩽ 50-W) bursts are associated with fewer complications [8, 19, 23].

The literature on bronchoscopic laser surgery is conflicting with respect to the optimum mode of ventilation and anaesthesia. Differing recommendations are made regarding local *v.* general anaesthesia, spontaneous *v.* controlled and (Venturi) jet *v.* bag ventilation. Differences regarding the efficiency of ventilation may stem from variations in patient selection, pulmonary pathology (type, location, pulmonary function), partial obstruction of the lumen of the ventilating channel by flexible bronchoscopes or instruments, and use of different types of jet and bag ventilation techniques. The description of the instrumentation and the technique of ventilation and its efficacy are often minimal; consequently, the characteristics of ventilation are difficult to evaluate from the literature, for example the report of Perera and Mallon [62]. Several large series of YAG applications via the rigid bronchoscope allude to achieving satisfactory ventilation as assessed only by adequate oxygenation [19].

Methods of ventilation during rigid bronchoscopy have been examined by many authors; this has led to the development of various approaches, including side-arm bag, jet and "high frequency" ventilation [10, 29, 70, 71, 94, 95]. Tracheal catheters are also used for rigid bronchoscopy; they have been discussed above. Mild hypercapnia has been associated with ventilation through a tracheal tube during flexible bronchoscopy in addition to side-arm bag ventilation via the rigid bronchoscope [9, 17, 98]. The anaesthetist's ability to assess the delivery of an adequate tidal volume by side-arm bag ventilation has been questioned [29, 51]. Hypercapnia during bag ventilation has led other practitioners to favour jet ventilation during bronchoscopic laser surgery [62]. In the case of the bronchoscope, efficacy of ventilation depends on the site of jet entry, the amount of entrainment possible, the type of rigid bronchoscope used, its diameter, length and shape, and the space left in the working channel after instruments, telescopes or flexible bronchoscopes have been inserted [50]. The latter applies also to ventilation through the tracheal tubes and bag-via-side-arm ventilation with the rigid bronchoscope. Different siting of the jet, for example at the proximal end of an open-ended rigid bronchoscope [71] or at the distal end [94, 96], results in rather different gas dynamics, as illustrated by Conacher, Paes and Morritt [14]. If the jet exits in close proximity to tumour or the bronchial wall (increased resistance, reduced compliance), it may lead to back pressure in the Venturi system, diminishing ventilation [35]. If the method of jet ventilation relies not at all or only minimally upon entrainment of ambient gas, driving pressures need to be high enough to deliver an adequate volume of ventilation unless "high frequency" ventilation is used [39, 84]. Jet flow depends on the diameter and length of the injection assembly and on the type, density and viscosity of the gas mixtures. Satyanarayana and colleagues required a driving pressure of 345 kPa (≃50 lb in^{-2}) to establish adequate ventilation through the working channel of a flexible bronchoscope (68 cm long, 2 mm i.d., inspired gas

100% oxygen) [72]. In this example of jet ventilation, no entrainment takes place and, by definition, it is not Venturi ventilation.

It is apparent that a variety of techniques provide satisfactory ventilation and surgical conditions, provided that the limitations of the techniques are realized. Vigilance is required, especially in view of the potential for hypoxaemia and hypercapnia. Bronchoscopic jet equipment should undergo systematic analysis of its flow, pressure and volume characteristics [53], but only a few systematic studies of ventilation through a bronchoscope under standardized conditions have been reported [35].

Rigid ventilating bronchoscopes have been adapted specifically for use during CO_2 and Nd–YAG laser bronchoscopy [14, 19, 78, 94]. These efforts have led to the commercial introduction of new rigid bronchoscopes designed specifically for the application of the CO_2 and Nd–YAG laser beam. The Wolfe–Dumon bronchoscope features two proximal ports, which immediately enter the main shaft, one for introduction of the laser fibre and one for a semi-rigid polymeric suction tube. A T-adaptor provides a swiveling side arm placed at a 90° angle to the shaft for bag or jet ventilation from each side of the operator of the bronchoscope; telescopes and forceps with cold light illumination are inserted in the usual manner [19]. Similarly, side-arm bag ventilation via a swivel adaptor placed at a 90° angle to the shaft can be managed from each side of the bronchoscopist in the Storz–Shapshay version. A separate jet arm at a 30° angle to the shaft is incorporated in the adaptor. Through the use of a proximal adaptor, which provides two metal channels, one for the laser fibre and one for the semi-rigid polymeric suction catheter, better control of the distal aspect of the fibre and the suction catheter is achieved [77]. Alternatively, an adaptor providing three ports without metal guiding channels can be used. Distal illumination is provided via a prism in the swivel adaptor as well as via the telescopes and forceps.

The Pilling Company produces a rigid bronchoscope for Nd–YAG laser application. It provides one channel (2.5 mm i.d.) for suction catheters and one 4-mm i.d. channel through which the largest YAG fibre equipped with a sapphire tip can be guided. The channels enter the main shaft 2 cm above the distal end of the bronchoscope, as does the separate cold light channel. The latter can also be used as a second suction or instrument channel. Illumination of the field is also provided by a cold light guide in the telescopes. A non-swivel side arm fixed at a 45° angle to the shaft allows both bag and jet ventilation. The fibre is directed by manipulation of the bronchoscope.

The Nd–YAG bronchoscopes have distal side vents to allow passage of gases if the bronchoscopic tip is obstructed. All three companies also market bronchoscopes for CO_2 laser beam application. No systematic evaluation of gas dynamics during jet or bag ventilation has been undertaken with these new bronchoscopes. A bronchoscope in which the jet enters the shaft distally, as proposed by Vourc'h, is not commercially available [94, 96].

Several authors have emphasized the need to maintain an inspired oxygen concentration of, at maximum, 40 or 50% during firing of the YAG laser [96, 98]. Absence of combustion and airway fires is in part attributed to this measure. It should be pointed out that this concentration of oxygen does support ignition and flammability of combustible material such as a polymeric tracheal tube, the flexible bronchoscope and a suction catheter [100]. When direct hits of the combustibles are avoided and the YAG fibre tip is kept clean, flushed and correctly applied, it is unlikely that a fire would occur under clinical conditions. When a rigid metal bronchoscope is used, the only combustible material available is the laser fibre itself and a suction catheter. Tissues and medical gases and anaesthetics do not form combustible material under non-hyperbaric medical conditions.

The inspired fraction of oxygen may be determined by the requirements of the patient. Dried carbonized particles may occasionally glow briefly, but without sequelae. The only reported YAG airway fire occurred in a patient with a tracheal tube, through which a flexible bronchoscope containing the laser fibre was advanced [13]. The inspired fraction of oxygen was intended to have been 0.4, but may have been 0.8; however, both concentrations are capable of supporting ignition and flammability of the polymers used [100]. Others, using the same equipment, have not experienced airway fires in the presence of an inspired oxygen fraction of 0.5 [8]. The "all metal" approach has not produced a fire [19]. In this case, prevention of a fire depends on maintaining the Nd–YAG fibre tip clean and flushed continuously with cooling gas (helium, helox, nitrogen, air), firing under "direct" vision and avoidance of impinging the beam on the suction catheter. The jet of gas also cools carbonized debris, reducing its potential for incandescence. If diluent gases are used to reduce the inspired fraction of oxygen, nitrogen or helium can be used. Helium enhances oxygen transport beyond narrow passages if turbulent flow occurs; it also has a greater heat capacity and conductance than nitrogen, and is therefore a better coolant.

General anaesthesia may be provided using i.v. or volatile anaesthetic agents with controlled or spontaneous ventilation through a rigid bronchoscope or tracheal tube [19, 96, 98]. I.v. techniques have been associated with prolonged recovery times, sedation and postoperative ventilatory depression, conditions which are of particular concern in patients with potential respiratory obstruction from oedema, bleeding, secretions, debris and residual pathology [18, 19, 75]. General anaesthesia is more readily controlled with inhalation anaesthetics and the trachea may be extubated with minimal residual depressant effects. Thus general anaesthesia with inhalation agents has distinct advantages [98]. However, with the development of shorter acting agents (alfentanil, sufentanil, midazolam) and an increase in experience, anaesthetic and surgical requirements can probably be well provided with an i.v. technique, with a reduction in complications [8]. I.v. anaesthesia is used mainly during bronchoscopic jet ventilation, although the entrainment of volatile agents has been suggested as an alternative [15, 40]. If entrainment of inhalation agents is required, the vaporizer output should be sufficiently high (up to 10%) to deliver adequate concentrations of halothane from the bronchoscope [15]. With the exception of the copper kettle, most vaporizers currently manufactured are incapable of such high outputs.

Clinical practice

The following account reflects our own clinical practice. Oxygenation is of prime concern in patients who frequently have a compromised airway with minimal ventilatory reserve. An inspired oxygen concentration of 30% is the lowest concentration that we use. In the absence of combustible material, the use of oxygen (or nitrous oxide) is not restricted, nor are the halogenated agents (halothane, enflurane and isoflurane). In our opinion, the need for an immobile surgical field and control of the airway and ventilation necessitates, with few exceptions, general anaesthesia with neuromuscular blockade. Anaesthesia is induced by the i.v. (barbiturates, benzodiazepines, opioids, etc.) or inhalation (halothane, enflurane) route. In this manner, a deep level of anaesthesia is obtained to minimize the cardiovascular responses during instrumentation of the airway. Arrhythmia or myocardial infarction may occur in response to suspension laryngoscopy and rigid bronchoscopy [88]. I.v. propranolol may be given before induction to attenuate the cardiovascular response to laryngoscopy [24]. Topical lignocaine, such as a 4% lignocaine spray applied to the laryngotracheobronchial tree at intubation, an i.v. bolus of lignocaine, or a 0.4% lignocaine infusion have also been used in an attempt to attenuate these responses [38, 86].

After induction of general anaesthesia or, very rarely, by awake intubation, we intubate the trachea with a regular, unwrapped polyvinylchloride (PVC) tube. After evaluation of the pathology, the ventilation technique best suited for the airway pathology and the surgical mode of treatment is selected; we prefer the use of metal instruments, including the metal tracheal tube, the operating laryngoscope with Venturi jet ventilation and the ventilating bronchoscope with side-arm bag or Venturi jet ventilation. The aluminium foil wrapped, red rubber or Xomed silicone tracheal tube is preferred for CO_2 laser surgery.

When Venturi jet ventilation through the laryngoscope is planned, the PVC tracheal tube is left in place until the patient is positioned with the suspension laryngoscope, the microscope and the Venturi jet needle in place. After a few jet trials, the PVC tube is removed from the airway and jet ventilation proceeds. This method provides early control of the airway and a smooth transition of ventilation technique [56]. One hundred percent oxygen is used and anaesthesia is maintained with an infusion of methohexitone (e.g. $100\ \mu g\ kg^{-1}\ min^{-1}$ during the first 3–5 min, followed by an infusion of $20–40\ \mu g\ kg^{-1}\ min^{-1}$), opioids (alfentanil, sufentanil, fentanyl), benzodiazepines (midazolam, diazepam), ketamine or droperidol, or both. An infusion of suxamethonium or a neuromuscular blocking agent of intermediate duration (atracurium, vecuronium) is often ideally suited for these procedures of unpredictable duration. At the end of the laser procedure we often reintubate the trachea with a PVC tracheal tube after the airway is cleared by suctioning. The trachea is extubated once spontaneous ventilation and appropriate reflexes have returned. Neonates and infants are also managed routinely with this technique, without the complications alluded to by Brummitt, Fearon and Brama [7]. Inadequate ventilation and intraoperative airway obstruction from instruments, debris and obstruction or displacement of the ventilating apparatus require constant vigilance.

In the case of application of the Nd–YAG laser beam to tracheobronchial pathology, a large ($\geqslant$ 8 mm i.d.) PVC tracheal tube with a swivel port (Portex) is used to allow initial inspection of the process with a flexible fibreoptic bronchoscope under general anaesthesia. However, preoperative evaluation of the airway pathology with the flexible fibreoptic bronchoscope is preferred. If manipulation of a large obstructive process is required to maintain an adequate airway, a rigid bronchoscope is used from the onset. For laser treatment of tumours of the trachea and mainstem bronchi, the rigid bronchoscope is used. General anaesthesia is induced as outlined above. We prefer side-arm bag ventilation for bronchoscopic procedures. Inhalation anaesthetics (halothane, isoflurane or enflurane) are added to oxygen, while helium or nitrogen is used as the diluent gas.

When obstructive pathology is accompanied by (intermittent) hypercapnia or hypoxaemia or both, we utilize up to 100% inspired oxygen or oxygen–helium mixtures. Flare-up of proteinaceous residue in the Nd–YAG laser beam is reduced by curtailing the content of oxygen (and nitrous oxide) and by the stream of cooling gas (nitrogen, helium, helox, air). The inhalation anaesthetics are supplemented with small doses of the short acting opioids or babiturates. Full muscle relaxation is provided with appropriate agents. At the end of the procedure the trachea is reintubated with a PVC tracheal tube, permitting optimal ventilatory control and cleaning of the airway.

After operation, elevation of the head and the sitting position aid lymphatic drainage and help to open up the air passages [22]. Swelling of the tongue and other oropharyngeal tissues is observed occasionally after suspension laryngoscopy. Nebulization of water in the inspired gas reduces drying of the oropharyngeal structures after laryngoscopy with Venturi jet ventilation [81]. The use of steroids to reduce oedema is controversial, but their anti-inflammatory action may be beneficial. Post-anaesthetic complications of Venturi jet ventilation are usually manifest within the first 2–4 h. Delayed complications produced by the different pathophysiology induced by the application of the Nd–YAG laser beam to tracheobronchial tumours can be encountered during the first 24 h after operation; these include ventilatory depression and obstruction, perforations resulting in haemorrhage, and pneumothorax; fortunately these complications occur only infrequently [76, 96, 98].

Management of intra-tracheal fires

Ignition of the tracheal tube and explosions, in addition to unintended facial burns, are the most common complications of the use of the CO_2 laser [26, 32]. The paucity of reports of tracheal tube fires in conjunction with the use of the Nd–YAG laser may stem, in part, from different application techniques [19]. For an explosion to occur, there must be a source of ignition (the laser beam), a source of combustion (for example an elastomeric tracheal tube or cottonoids) and a medium which supports combustion (such as oxygen or nitrous oxide). A laser-ignited explosion may lead to serious injury to the patient and the experience can devastate the operating room team [74].

A laser ignited explosion can cause a thermal and chemical injury. Thermal injury results from direct exposure to the flame. The severity of the burn depends on the duration of exposure and the heat intensity. The subglottic region, the epiglottis, the base of the tongue and the oropharynx are most likely to be affected. The flame may extend the length of the laryngoscope to burn the lips and face of the patient. Thermal injury can also result from heating of the tracheal tube, while burning tissue can be blasted into the distal airways. Inhalation of smoke may produce a chemical burn. Bronchospasm, intra-alveolar haemorrhage, oedema, and loss of surfactant may occur and lead to respiratory failure. Hydrogen chloride, a pulmonary toxin which produces a severe pneumonitis, is released when polyvinylchloride tubes burn [20, 99], while carbon monoxide is a decomposition product of burning rubber [33].

The anaesthetic and surgical team should be well rehearsed in the management of sudden fire and appropriate equipment should be immediately available. Initially, the source of oxygen and nitrous oxide should be disconnected, the tracheal tube removed rapidly and the area flushed liberally with sterile water or normal saline. A new tracheal tube should be inserted and ventilation resumed with 100% oxygen as indicated clinically. This assumes that intubation is easy; if this is not the case, a long stylet can be passed through the existing tube before removing it in order to facilitate the passage of a new one. When the fire is extinguished and the airway secured, rigid bronchoscopy with a ventilating bronchoscope can be performed. The extent of injury can then be assessed, foreign bodies (pieces of tube, aluminium foil, pledgets) removed, and the large airways washed to remove carbonaceous deposit. Subsequent management depends on the severity of the burn. The decision to extubate the trachea depends on clinical judgement.

Humidification of inspired gases is essential and a 24-h course of high dose steroids—methylprednisolone 5–7 mg kg^{-1} or dexamethasone 1–1.5 mg kg^{-1}—is recommended, although their efficacy has not been proven [30]. It may be appropriate to administer a course of antibiotics. Recovery can be monitored by flexible or rigid bronchoscopy and this helps to determine the optimal time for extubation. Supportive measures, such as intermittent positive pressure ventilation and monitoring of pulmonary artery pressures, cardiac output and oxygenation (pulse oximetry), may be necessary. Tracheotomy may also be required.

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PREOPERATIVE INTERCOSTAL NERVE BLOCK: EFFECT ON THE ENDOCRINE METABOLIC RESPONSE TO SURGERY

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The endocrine metabolic response to surgery is triggered by various stimuli, including afferent neuronal activity from the site of tissue damage. This initiates a train of events with widespread hormonal and metabolic sequelae. Many factors affecting this response have been revealed by blocking afferent neural pathways and assessing the degree of attenuation of the response.

Most of the work in this field has utilized extradural analgesia. There are no data on the effects of intercostal blockade on the glucose and cortisol response to surgery and we have studied this in patients undergoing cholecystectomy.

METHODS AND RESULTS

Twenty patients (ASA categories I or II and free from endocrine or metabolic disorders) were studied. All were to have cholecystectomy performed by one of two surgical teams. Hospital Ethical Committee approval was gained and informed consent obtained from all patients.

Patients were allocated randomly to one of two groups, group A receiving the intercostal blocks, group B receiving the same anaesthetic technique without the blocks. Premedication comprised diazepam 10 mg by mouth 1 h before the procedure. Upon the patient's arrival in the anaesthetic room 16-gauge cannulae were inserted into both arms under local anaesthesia. Samples for baseline glucose and cortisol concentrations were taken and midazolam 2.5–5 mg administered i.v. ECG electrodes were applied and connected to a 24-h ambulatory recorder.

Patients receiving the intercostal blocks were turned prone and further midazolam 5–7 mg administered to produce a light sleep. The blocks were performed 7 cm from the midline bilaterally according to the technique described by Moore [1]. Seventy millilitre of 0.5% bupivacaine (350 mg) was used with adrenaline 250 µg added; 5 ml was injected at each rib. On completion of the blocks the patients were returned to the supine

SUMMARY

The plasma cortisol and glucose responses to cholecystectomy were studied in 20 healthy patients. Ten patients received preoperative intercostal nerve blocks of the 6th to 12th nerves bilaterally using 0.5% bupivacaine with adrenaline 250 µg. The control group had the same quantity of adrenaline infiltrated into the intercostal space. Both groups had general anaesthesia with endotracheal intubation and controlled ventilation. In the non-blocked group, the mean cortisol concentration increased from a control value of 182.5 nmol litre^{-1} to a peak of 686.2 nmol litre^{-1} at 5.5 h after incision. In the blocked group the baseline serum cortisol concentration was 283.8 nmol litre^{-1} and it increased to a similar peak at 5.5 h. There were no significant differences between groups. The baseline plasma glucose concentration was also higher in the blocked group (4.45 mmol litre^{-1} compared with 3.94 mmol litre^{-1}), but after a brief increase following the performance of the block decreased to only 14% above control values. The unblocked group exhibited a substantial increase following the start of the surgery which continued for the duration of the study period to end at a mean of 6.48 mmol litre^{-1}. These differences were significant ($P < 0.001$). It is concluded that bilateral intercostal blocks may inhibit the glucose response to surgery, but have no effect on the cortisol response.

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position and anaesthesia was induced with thiopentone 4 mg kg^{-1}. Intubation of the trachea was facilitated by suxamethonium 1 mg kg^{-1}. In patients not receiving the intercostal blocks, anaesthesia was induced in a similar fashion and the same amount of adrenaline was infiltrated into the intercostal muscles following induction. In both groups ventilation was controlled, the intercostal group receiving no neuromuscular blocking drug unless surgical relaxation proved inadequate or unwanted patient movement occurred. In both groups anaesthesia was maintained by nitrous oxide in oxygen and 0–2 % enflurane as required. Blood samples for measurement of cortisol and glucose were taken on arrival in the anaesthetic room and at the following times after incision: 1, 30, 90, 150, 210, 270, 390 min.

Cortisol assay was performed using a radioimmunoassay technique.

Glucose was assayed enzymatically using a Technicon AA2 autoanalyser (glucose oxidase and 4 amino phenazone).

Compound sodium lactate solution was infused at a rate of 5 ml kg^{-1} h^{-1} for the duration of the operation and for 4 h thereafter in both groups. Subsequently 4 % dextrose in 0.18 % saline was infused at 100 ml h^{-1}.

The data were analysed using the GLIM program. After testing for normality, data were compared by regression analysis and F tests.

The two groups did not differ significantly in respect of age, size, duration of surgery, or blood loss. Attention was paid to the following aspects of the study design.

Haematocrit. The haematocrit of the cortisol samples was measured. The variation between samples was not more than 5 %.

Duration of starvation. The patients were always first on the operating list to ensure uniformity of fasting.

Adequacy of blockade. The extent of the block was assessed on wakening by loss of cutaneous sensation to pinprick. One patient who had severe pain on recovery from anaesthesia and an inadequate block was excluded from the study.

Cardiovascular variables. The intercostal group exhibited very stable cardiovascular systems with little change in heart rate or arterial pressure. The unblocked group had higher heart rates and arterial pressures at comparative sampling times. They thus required higher concentrations of enflurane to maintain anaesthesia.

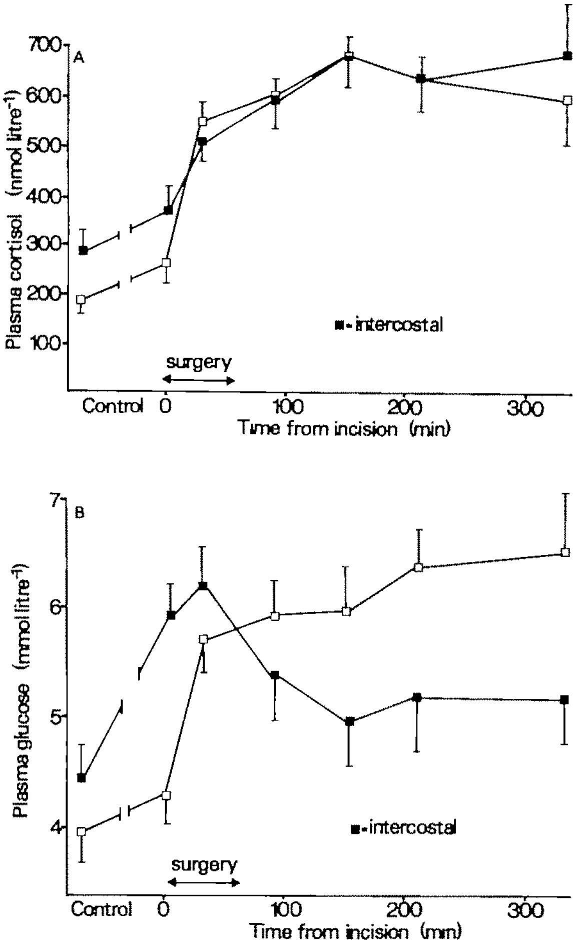

FIG. 1. Changes in plasma cortisol (A) and glucose (B) concentrations. The duration of surgery is indicated by the horizontal arrow. Closed squares represent intercostal block group, open squares control group. Mean ± SEM.

The baseline plasma cortisol concentration was initially higher in the intercostal group. Following the onset of the surgery there was a rapid increase in both groups to a plateau after 3 h. There were no significant differences between the two groups, but there was a significant change from the baseline value (fig. 1A).

The baseline plasma glucose concentration was initially higher in the intercostal group. In this group there was an increase with performance of the blocks, but after a peak 1 h after the block, the concentration decreased to a plateau at a mean value 14 % above the control value. In the unblocked group a similar charge occurred, but it was delayed until the onset of surgery, and the value continued to increase for the duration of sampling to a level 64 % above the control value.

There was a significant difference between the two groups ($P < 0.001$) (fig. 1B).

COMMENT

The results of this study show that blockade of the intercostal nerves before operation produces a diminution in the glucose response to cholecystectomy, but does not affect the cortisol response. Whilst it may be said that the groups were poorly controlled, in that the control group had neither a sham block procedure nor similar plasma bupivacaine concentrations, it was not thought ethically justifiable to perform these manoeuvres.

Under general anaesthesia the plasma glucose and cortisol concentrations increase soon after the commencement of surgery and remain abnormally increased for several hours. The changes in both these variables can be modified substantially by extradural analgesia following lower abdominal surgery [2], while only the glucose response is influenced by a similar block following upper abdominal surgery [3]. It is thus not suprising that this study has failed to show any alteration in cortisol response.

However, we have shown that intercostal block modified the glucose response, but only after a significant increase just before incision. This is most likely to be a result of the stimulus of performing the block. The injected adrenaline may have caused an increase in glucose concentration, but this was also administered to the control group in whom a change was not seen until the start of surgery.

Patients who have had uncomplicated abdominal surgery with intercostal blocks may be virtually pain free on recovery from anaesthesia, thus the major nociceptive component of the stimulus is abolished by somatic block of the intercostal nerves. For the glucose response to be modified, however, some blockade of the sympathetic nervous system must be postulated. Intercostal blocks have been shown, by dye and radiographic studies [4], to extend medially as far as the sympathetic chain, especially with the large volumes used in this study. Thus it is possible that we have induced a block similar in extent and nature to thoracic extradural block which would explain the similarity to the results of Bromage [3] and the ablated cardiovascular responses we noted.

Control concentrations of both glucose and cortisol were higher in the intercostal group. It may be that this is a chance occurrence, but a possible explanation is the increased anxiety of the patients anticipating the block. Psychological stress has been shown to affect some hormonal concentrations [5].

The large dose of bupivacaine injected produced high plasma concentrations, but no side effects were noted. This is consistent with the wide experience of one of the authors (L.D.B.) in injecting similar doses in the intercostal space without untoward sequelae. It is possible that these high concentrations could have been responsible for some of the changes seen, but available evidence suggests this is unlikely. Birch and colleagues [6] found no effect of i.v. lignocaine on cortisol or glucose responses and we found no correlation between the increase in plasma bupivacaine concentrations and the decrease in plasma glucose concentrations.

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GRAND MAL SEIZURE AFTER EXTRADURAL MORPHINE ANALGESIA

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SUMMARY

Following an elective Caesarean section under extradural anaesthesia, a 30-yr-old known epileptic woman (gravida 4, para 3) developed a tonic–clonic seizure, 6 h after the administration of morphine 3 mg into the extradural space. Possible aetiological factors are discussed.

Major advances have been made in our understanding of the sites and mechanisms of action of opioid agents [1,2]. Recent reports indicate that effective and prolonged pain relief can be obtained in man by the injection of small doses of morphine or pethidine into either the subarachnoid [3] or the extradural space [4]. As a result, extradural morphine analgesia is being used increasingly by clinicians [5, 6], especially in obstetrics and gynaecology [7]. Side effects attributed to extradural morphine are common, possibly dose-related and include nausea and vomiting, pruritus, urinary retention and (more rarely) early and late respiratory depression [8]. Seizure, a theoretical complication of intraspinal administration of opioids [9], has been reported only once before and it happened after what was probably a high pressure intrathecal injection in a patient with known metastatic breast cancer [10]. We report the case of a patient who developed a generalized tonic–clonic seizure 6 h after the administration of morphine 3 mg into the extradural space.

CASE REPORT

A 30-yr-old woman (gravida 4, para 3), weighing 75 kg, was referred to our department for an elective Caesarean section as an ultrasound scan had shown the presence of twins in the breech position at 37 weeks gestation. The actual pregnancy was free of incident; there was no hypertension, oedema or proteinuria.

At the age of 19 yr the patient had suffered her first grand mal seizure. Investigations did not reveal any brain lesion and she had no family history of epilepsy. From that time, she was treated with phenobarbitone 175 mg daily, and suffered one or two grand mal fits each year up to the age of 26 yr. She had had an uneventful pregnancy terminated by forceps delivery under extradural bupivacaine analgesia at age 29 yr.

It was decided to utilize extradural anaesthesia. Ringer's solution 1500 ml was infused and the patient was placed in the left lateral decubitus position. Using the "loss of resistance" technique, the extradural space was entered at L2–3 with an 18-gauge Tuohy needle and the catheter was advanced 5 cm cranially without difficulty. An aspiration test revealed neither blood nor CSF and 1% lignocaine 2 ml was injected through the catheter. As neither motor nor sensory deficit occurred, a second aspiration test (also negative) was carried out 5 min later and 2% carbonated lignocaine 20 ml (Astra) with freshly added adrenaline 0.1 mg was injected at a rate of 5 ml min^{-1}. The resulting sensory block extended to T5 on both sides. Two male infants (2440 and 2540 g) were delivered with Apgar scores of 8/9/10 and 7/9/10, respectively. A bilateral tubal ligation was performed and a continuous infusion of oxytocin (10 u. in 5% glucose 500 ml over 12 h) was started.

At the end of the procedure and following a negative aspiration test, 3 mg of preservative-free morphine (Vifor, Geneva) was administered in 10 ml of physiological saline via the extradural

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catheter. The immediate postoperative period was uneventful. Analgesia was satisfactory, the rate of ventilation was within the normal range and normovolaemia (as assessed by diuresis and central venous pressure) was maintained. Four hours after the administration of the extradural morphine, a slight pruritus of the face and the neck was noted, but this was not severe enough to necessitate medical treatment. Two hours later, without alterations in vital signs or warning symptoms, the patient suffered a generalized tonic–clonic seizure with loss of consciousness. The plasma concentration of phenobarbitone (16.2 $\mu g\ ml^{-1}$) was within the therapeutic range and close to that measured at 25 weeks gestation (17.1 $\mu g\ ml^{-1}$). An EEG performed 3 days later was characterized by a diffuse and non-specific abnormal tracing.

DISCUSSION

Grand mal seizures can be precipitated by a number of factors, including certain drugs and pregnancy [11]. The increase in seizure frequency reported in pregnancy is thought to be the result of a pregnancy-associated alteration in the kinetics of antiepileptic agents, causing a decrease in the plasma concentration. When dosage was adjusted to maintain plasma concentrations in the therapeutic range, no increase in seizure frequency was observed [12]. In this patient, the plasma concentration of phenobarbitone was in the therapeutic range. Furthermore, with the same therapeutic regimen, the patient had suffered no seizure during the previous 4 yr, despite another pregnancy terminated by forceps delivery under extradural bupivacaine analgesia 1 yr before the event reported here.

Experimentally, the intracerebroventricular or intrathecal administration of morphine possesses convulsant properties [13, 14], in contrast to i.v. morphine, which has been used to suppress convulsions in eclampsia [15]. Bromage and colleagues [16] have shown cervical and intracranial spread of morphine injected into the lumbar extradural space in man and have observed a time-lag of approximately 6 h for the drug to reach the brain stem and the fourth ventricle.

The poor lipid-solubility of morphine, with its consequential restriction to CSF, implies a high concentration of free drug. Thus, the CNS irritating properties of morphine may have been enough to initiate a grand mal seizure in a patient whose trigger threshold was already low. The 6-h delay between the administration of the morphine and the onset of seizure in our patient is consistent with the known kinetics of morphine in the CSF [16, 17]. Factors known to induce seizures, such as pain, hyper- or hypoventilation or hypervolaemia, were all absent and cannot be considered contributory factors in this patient. Moreover, the penetration of morphine into the CNS was heralded by the development of pruritus, known to be one of the earliest side-effects of extradural morphine.

Although lignocaine, with its known central nervous system toxicity [18], either alone or by interacting with morphine [19], might have played a role in this patient, the absence of other CNS symptoms of lignocaine toxicity, such as dizziness, auditory and visual disturbances, coupled to the rather long delay between the administration of the lignocaine and convulsions (8 h) [20] argue against such a role.

In conclusion, although extradural morphine administration greatly improves the comfort of the patient after Caesarean section, its administration to epileptic patients might be questioned and should at least be monitored carefully.

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PERFORMANCE OF TRANSCUTANEOUS Po_2 AND Pco_2 DUAL ELECTRODES IN ADULTS

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SUMMARY

Three commercially-available combined PO_2–PCO_2 *electrodes were assessed* in vitro*, and in adults breathing air, hypoxic and hypercapnic mixtures, for speed of response, correlation with end-tidal gas tensions and drift. Differences in the 90% response time of the individual electrodes were more marked* in vitro *than* in vivo. *Changes in end-tidal gas tensions were reflected by proportionate changes in transcutaneous oxygen and carbon dioxide (*Ptc_{O_2} *and* Ptc_{CO_2}*) but, in the individual subject,* Ptc_{O_2} *and* Ptc_{CO_2} *were generally poor indicators of the end-tidal values. During steady-state recordings, the* Ptc_{O_2} *signal drifted upwards by more than 12 mm Hg during 140 min* in vivo *recording in all three electrodes, without changes in either* Ptc_{CO_2} *or end-tidal values. The dual electrodes tested provide non-invasive estimates of qualitative, but not quantitative, change in blood-gas tensions and are likely to have only a limited role to play in adult anaesthetic practice.*

Systems permitting the transcutaneous monitoring of blood-gas values are used widely in neonatal intensive care units. Improvements in electrode and monitor design, simplified calibration procedures and the arrival of the combined oxygen and carbon dioxide electrode [1] are likely to increase their use in operating theatres and adult intensive care units [2]. The ideal monitor should be easy to use and calibrate, accurately reflect changes in arterial blood-gas tensions, and have little drift of its own [3]. How good are current combined transcutaneous monitors? The earlier models of dual electrodes provided transcutaneous oxygen and carbon dioxide (Ptc_{O_2} and Ptc_{CO_2}) values which were highly correlated with blood-gas tensions in infants [4]. Relatively few data on the performance of this type of device in adults exist to guide one's choice of presently available commercial systems.

SUBJECTS, MATERIALS AND METHODS

Methods

We evaluated three commercial dual electrodes (Microgas Combisensor, Kontron Ltd; Novametrix 850 Commonsensor, Vickers Medical Ltd; and Radiometer E5270 electrode, V.A. Howe Ltd) in normal adults as follows: (A) an *in vitro* assessment of the response times and stability of the electrodes; (B) an *in vivo* assessment of response times, accuracy and drift of the dual electrodes compared with end-tidal gas concentrations.

Twelve non-smoking healthy adults (7 male; ages 23–48 yr) recruited from both Departments following informed consent, took part in the investigation, which had the approval of the hospital Ethics Committee. Each electrode was used within 5 days of being remembraned, and was given a 2-point dry gas calibration at 45 °C before use according to manufacturers' instructions, which allowed for barometric pressure and the "gas/skin ratio". Electrodes were exposed to a certified gas calibration standard (5% carbon dioxide + 12% oxygen + 83% nitrogen, Corning Medical Ltd) before and after each study; we defined a "calibration shift" as the difference between these two *in vitro* readings. The electrodes were fixed to the skin over the biceps using double-sided adhesive rings, after the skin was cleaned with alcohol, rubbed until red, and contact liquid applied. The electrodes were operated at 45 °C and allowed to stabilize for 30 min before recordings were made. Arterial blood-gas

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values were estimated by averaging peak and trough end-tidal concentrations ($P\text{E}'_{CO_2}$ and $P\text{E}'_{O_2}$) over 2 min [5] in expired gas sampled through a fine-bore tube taped to the nose or mouthpiece. The use of end-tidal gas avoided the hazards of arterial cannulation, yet provided values which closely reflect arterial blood-gas tensions in normal subjects [5, 6]. Gas concentrations were measured by a quadrupole mass spectrometer (MGA 2000, Airspec Ltd, drift < 0.1 % per hour), previously calibrated using room air and a certified gas mixture as for the electrodes, and correcting for barometric pressure; the arterio–alveolar difference for oxygen was assumed to be 5 mm Hg breathing 21 % oxygen and 0 mm Hg breathing hypoxic gases. The analogue outputs from the monitors and mass spectrometer were displayed on a six-channel recorder (Linear Chartrecorder Ltd) with a paper speed of 5–25 mm min^{-1}.

Procedures

In vitro studies. The three electrodes were mounted on a template and allowed to stabilize in room air before rapid insertion into a 100-ml pot receiving a constant flow of the gas calibration standard. Once readings were stable (< 3 min), the electrodes were rapidly removed and re-exposed to air. The procedure was repeated six times. We defined the lag time as the time interval (s) between changing the gas tensions and the first detection of that change by the electrodes, and the 90 % response time (90 % RT) as the time interval (s) between detecting and reaching 90 % of the change in partial pressure caused by the step change in gas tension [7]. Before and after each *in vivo* study, each electrode was placed in a cuvette, perfused with the certified gas mixture, and allowed to reach a steady-state reading for estimation of the calibration shift.

In vivo studies. The subjects were seated comfortably on a couch breathing air or, on separate days, hypoxic or hypercapnic mixtures through a two-way valve from a 250-litre Douglas bag. Steady state values for $P\text{tc}_{O_2}$, $P\text{tc}_{CO_2}$, $P\text{E}'_{O_2}$ and $P\text{E}'_{CO_2}$ were averaged over 2 min in 12 subjects breathing air, eight breathing a hypoxic mixture for 12 min (mean inspired oxygen = 12.8 %, range 11.8–13.5 %) and eight breathing a hypercapnic mixture for 8 min (mean inspired carbon dioxide = 5.9 %, range 4.2–6.7 %). The lag and 90 % response time were recorded, as previously defined. On a separate occasion, 30 min after applying the electrodes, *in vivo* drift (= *in vivo* change from baseline values with time) was calculated by averaging transcutaneous and end-tidal values over 4 min at eight consecutive 20-min intervals in six resting subjects breathing air (total time 2.5 h).

Analysis

The relationship between transcutaneous and end-tidal values was assessed using least squares regression equations and calculating the correlation coefficients for each electrode. To minimize bias, we analysed only one pair of measurements in each subject from each steady-state condition, and at set time intervals unknown to the subjects. In addition, the average difference between the two measurements and the 95 % confidence limits for that difference were calculated and plotted against the average measurement of oxygen and carbon dioxide [8, 9]. Finally, differences between electrodes were assessed using the paired Wilcoxon signed rank test with a statistical significance value of $P < 0.05$.

RESULTS

In vitro studies

The lag and 90 % response times for the three dual electrodes were greater for carbon dioxide than for oxygen (table I). Changes in oxygen were detected most rapidly by the Novametrix electrode—the 90 % response time was two to three times shorter than with the other electrodes ($P < 0.01$). A reduction in carbon dioxide tension was most rapidly detected by the Radiometer electrode, while an increase in carbon dioxide was more rapidly detected by the Novametrix electrode. The Kontron electrode was the slowest to detect changes in all situations. There were minimal calibration shifts for the three electrodes following the *in vivo* studies: Kontron +2.7 (3.3), Radiometer +1.8 (2.8), and Novametrix −0.2 (2.3) for oxygen, and −0.67 (1.0), −0.2 (0.8), and +1.0 (2.5) for carbon dioxide (mean values (SD) in mm Hg), respectively.

In vivo studies

The lag and 90 % response times were much greater *in vivo* than *in vitro*, and the 90 % response times were greater for oxygen than for carbon dioxide (table II). Lag times ranged from 23 to 36 s for changes in oxygen, and from 31 to 56 s for carbon dioxide. In all instances, 90 % response

TABLE I. In vitro *response to changes in blood-gas tensions (mean* ± 1 *SD*; n = *6). RT = Response time*

	Oxygen				Carbon dioxide			
	Change from 21 to 12%		Change from 12 to 21%		Change from 5 to 0%		Change from 0 to 5%	
Electrode	Lag (s)	90% RT (s)	Lag (s)	90% RT (s)	Lag (s)	90% RT (s)	Lag (s)	90% RT (s)
Novametrix	1.9±0.8	8.8±3.2	2.0±0.8	5.0±0.6	3.9±0.1	30.9±5.1	9.6±1.2	27.9±2.7
Radiometer	3.2±0.7	17.9±2.9	3.0±0.5	15.8±2.3	4.0±0.4	18.5±1.1	7.2±0.6	40.5±2.5
Kontron	4.2±0.4	20.3±5.2	3.5±0.7	16.7±0.6	4.5±1.1	51.3±1.3	17.1±1.6	52.8±1.9

TABLE II. In vivo *lag and* 90% *response times for change in inspired gas concentrations (mean* ± *SEM)*

	Oxygen				Carbon dioxide			
	Air to hypoxia		Hypoxia to air		Hypercapnia to air		Air to hypercapnia	
Electrode	Lag (s)	90% RT (s)	Lag (s)	90% RT (s)	Lag (s)	90% RT (s)	Lag (s)	90% RT (s)
Novametrix	30±1.3	264±21.8	23±3.7	302±18.4	31±3.3	58±11.6	44±5.9	140±29.8
Radiometer	35±4.2	279±41.5	25±3.7	317±24.2	33±3.1	61±14.2	45±4.5	160±30.5
Kontron	36±2.8	261±36.1	29±1.3	315±40.7	38±4.8	82±21.0	56±4.5	131±21.1

times were faster for carbon dioxide than for oxygen: 58–160 s compared with 261–317 s. Finally, differences in 90% response time between the dual electrodes were more variable and less marked *in vivo* than *in vitro*. The lag time between a change in the inspired mixture and a change in the end-tidal value was 5–7 s (or one breath interval) for both $P\text{E}'_{O_2}$ and $P\text{E}'_{CO_2}$. End-tidal gases stabilized at the new value within 300 s.

$P\text{tc}_{O_2}$ was closely correlated with $P\text{E}'_{O_2}$ for all three electrodes, but underestimated $P\text{E}'_{O_2}$ by an average of 8.9–11.4 mm Hg (table III). However, the $P\text{tc}_{O_2}$ value recorded by the three electrodes was highly variable in any one individual; while the 95% confidence intervals for the average difference between $P\text{tc}_{O_2}$ and $P\text{E}'_{O_2}$ recorded by any one electrode using group data were −15 to +33 mm Hg at best. In contrast, $P\text{tc}_{CO_2}$ values were much closer to $P\text{E}'_{CO_2}$: the Kontron electrode recorded values which, 19 times out of 20, were between −5.6 to +4.7 mm Hg of the observed $P\text{E}'_{CO_2}$ value. The results for the other two electrodes were less good, but in keeping with other reports [10].

$P\text{E}'_{O_2}$ and $P\text{E}'_{CO_2}$ remained stable during the *in vivo* drift study: baseline values (in mm Hg and with SD in brackets) were 99 (4.8) and 41 (4.0) for oxgyen and carbon dioxide, respectively, with maximum 4-min average changes during the study of −2.0 to +3.5 mm Hg for oxygen and −2.0 to +1.0 mm Hg for carbon dioxide. However, $P\text{tc}_{O_2}$ values increased significantly in all three electrodes ($P < 0.01$), reaching a plateau between 100 and 120 min for the Novametrix and Radiometer electrodes (fig. 1). These increases were present despite an initial stabilization period

TABLE III. *The relationship and differences between transcutaneous and end-tidal values.* n = *number of paired samples*; a, b = *intercept and slope for regression equation where* $\text{Ptc}_{O_2} = a + b\ (\text{PE}'_{O_2})$ *mm Hg*; r = *correlation coefficient,* $P < 0.001$; d = *mean difference* = $\text{PE}'_{O_2} - \text{Ptc}_{O_2}$ *mm Hg*; d+2s = 95% *confidence intervals for the mean difference*; **P <0.02

	Oxygen							Carbon dioxide						
Electrode	*n*	*a*	*b*	*r*	*d*	*d*+2*s*	*d*−2*s*	*n*	*a*	*b*	*r*	*d*	*d*+2*s*	*d*−2*s*
Novametrix	26	13.4	0.75	0.88	11.4	41.0	−18.2	20	13.8	0.69	0.52**	0.0	15.7	−15.7 *
Kontron	27	−11.3	1.03	0.94	8.9	32.9	−15.0	20	11.8	0.74	0.91	−0.5	5.2	−6.1
Radiometer	25	−14.0	1.04	0.93	10.0	35.2	−15.2	18	19.7	0.70	0.85	−6.6	0.2	−13.4

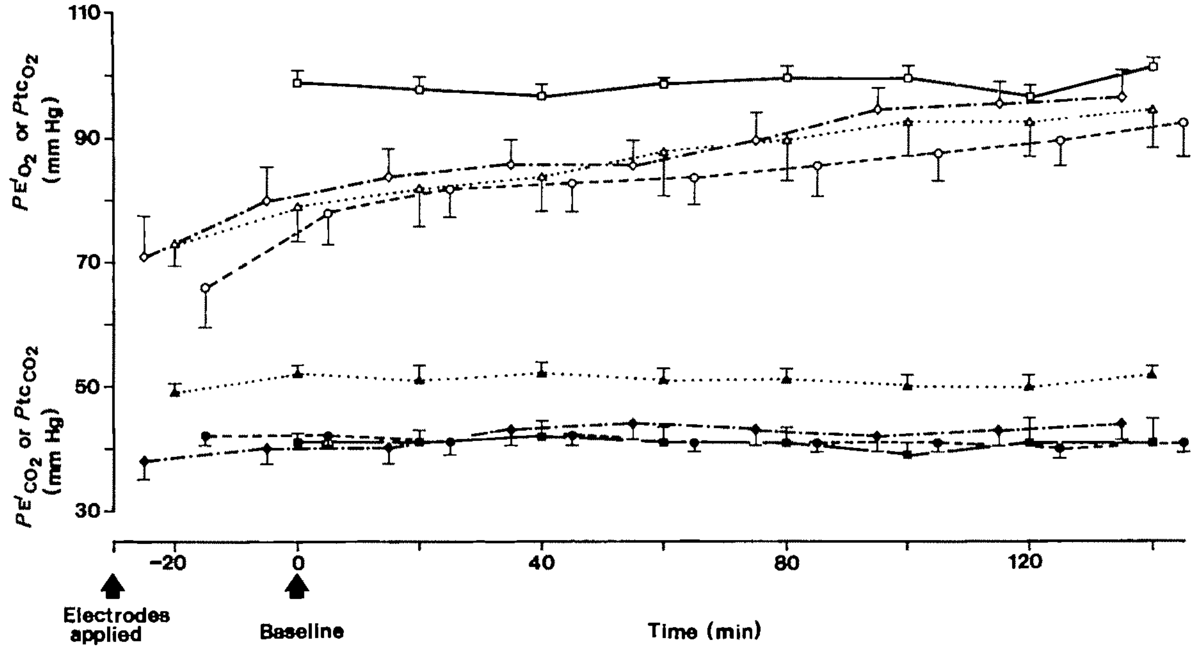

FIG. 1. Steady-state end-tidal (□/■) and transcutaneous values for oxygen and carbon dioxide. Mean values for six adults. Bars represent SEM. Open symbols = oxygen; closed symbols = carbon dioxide. Novametrix = ◇/◆; Radiometer = △/▲; Kontron = ○/●.

of 30 min, and were not accounted for by *in vitro* calibration shifts of the electrodes. In contrast, Ptc_{CO_2} remained fairly stable during the study (fig. 1).

All subjects reported mild redness of the skin for at least 24 h following the studies. From a total of 66 electrode applications, only one application caused a significant skin burn, with blistering and scarring over a 0.5-cm² area.

DISCUSSION

Combined sensors to measure P_{O_2} and P_{CO_2} were described first in 1979 [1, 11], but the production of hydroxyl ions at the oxygen electrode affected the stability of the P_{CO_2} reading [10]. Changes in the design of the electrode and the use of different electrolyte solutions have improved their performance [10, 12]. Using single electrodes, the greater differences between Ptc_{O_2} and Pa_{O_2} recorded in adults, compared within infants, have been explained by differences in electrode methodology [13], skin thickness [14], skin metabolism [15], cardiac output and peripheral perfusion [16].

Estimation of Pa_{O_2} *from* Ptc_{O_2}

Transcutaneous gas tensions are not simply non-invasive measures of arterial gas tensions, but also reflect cardiac output [17], local skin metabolism [15] and capillary blood flow [16]. Nevertheless, under stable haemodynamic conditions, transcutaneous gas tensions are widely used as trend monitors of arterial blood-gas tensions [18]. Differences between the two sets of tensions have been reduced by better electrode design and empirical readjustment of the *in vitro* calibration settings [19]. However, the differences between Ptc_{O_2} and Pa_{O_2} cannot be eliminated entirely, because of the nature of the technique [20]. The underestimation of $P\text{E}'_{O_2}$ by the three dual electrodes is unlikely to be the result of an overestimation of the true Pa_{O_2} by $P\text{E}'_{O_2}$ and is in keeping with reports using single [18, 20, 21] and dual electrodes in adults [22]. Indeed, the mean difference between age-predicted Pa_{O_2} [23] and observed $P\text{E}'_{O_2}$ was only 3.2 mm Hg. In contrast, the range of the difference between Ptc_{O_2} and $P\text{E}'_{O_2}$ in the individual was considerable: consequently, Ptc_{O_2} should not be used alone to estimate Pa_{O_2} in the adult [20]. Nevertheless, large changes in $P\text{E}'_{O_2}$ over the range 42–145 mm Hg were invariably detected by all three electrodes.

Estimation of Pa_{CO_2} *from* Ptc_{CO_2}

Ptc_{CO_2} will overestimate Pa_{CO_2} in adults [24] despite excellent correlation between the two, because the final Ptc_{CO_2} value is dependent on: (1) the carbon dioxide content of capillary blood; (2) the solubility of carbon dioxide in plasma; (3) the increased metabolism and shift of the carboxyhaemoglobin curve produced by the heating electrode; (4) cooling of the pH-sensitive glass electrode by the skin [25]. These factors combined to give a Ptc_{CO_2} reading which was higher than Pa_{CO_2} values [26], but could be corrected by adjusting the *in vitro* calibration settings [24, 27]. Our results indicate that dual electrodes produce Ptc_{CO_2} readings which closely reflect $P\text{E}'_{CO_2}$ values under steady state conditions.

In vivo response times

The *in vivo* response time of the transcutaneous electrodes was more than one order of magnitude slower than the *in vitro* responses, which suggests that, in practice, the former depends almost entirely on local perfusion factors. Faster response times are seen with higher electrode operating temperatures [28, 29] but, in general, this subject has received relatively little attention [7, 30]. A sudden change of inspired gases is the nearest approximation to a step change in partial pressures in capillary blood-gas tensions for testing the response time of the electrodes [31]. Rapid occlusion of the arterial blood supply to the arm is an alternative which likewise produces a ramp rather than a step change [7]. Neither technique indicates how quickly the sensor can detect a sudden change in arterial blood-gas tensions alone, but the former more closely simulates how quickly anaesthetic mishaps can be detected.

An interesting finding, previously noted by other workers [7], was that a change from air to hypoxia was more rapidly detected than a change from hypoxia to air. This may reflect changes in ventilation and cardiac output—variables which were not assessed in this study. In part, the shorter response times for carbon dioxide compared with oxygen can be attributed to increased capillary perfusion, cardiac output and minute ventilation caused by hypercapnia, and the more rapid diffusion of carbon dioxide across the skin. Nevertheless, these results indicate that, in adults, sudden changes in either Pa_{CO_2} or Pa_{O_2} are unlikely to be fully recorded using transcutaneous dual electrodes until 3–5 min has elapsed. The *in vivo* response time of the electrodes should be considered when alarm limits for these monitors are being set by the operator.

Ptc_{O_2} *drift*

Drift is analogous to very low frequency "noise" and, in our study, implies change in measurement over the course of hours without a corresponding change in "signal". It is only of interest in the long-term estimation of Pa_{O_2} and Pa_{CO_2} from transcutaneous tensions. The *in vitro* drift of a dual electrode is influenced by the electrode design, the electrode membrane and the electrolyte composition [10] and is usually less than 1 % h^{-1}. Calibration shifts reported in clinical studies may be much greater than *in vitro* drift values [29], being influenced by both the application and removal procedure of the electrode at the measuring site [32]. In our study, the calibration shifts were very small, which makes it difficult to attribute the recorded upward trend in Ptc_{O_2} to the electrode itself. Assuming that blood-gas tensions vary little at rest [33], that variations should occur randomly over time, and that variations in blood-gas tensions are detected by end-tidal measurement, the observed upward trend in Ptc_{O_2} must be the result of a change at the skin measurement site. This is supported by the finding that the change was not matched by a corresponding change in Ptc_{CO_2}. Increases in local capillary perfusion [20] and decreases in local tissue oxygen consumption as a result of thermal injury [15] would affect Ptc_{O_2} more than Ptc_{CO_2}, and might explain the results. However, the prerequisite for Ptc_{O_2} measurement is indeed a "limited" thermal injury—that is, heat-induced hyperaemia—and the electrode temperature used is a compromise between producing sufficient hyperaemia and avoiding burning [34].

Systems based on transcutaneous dual electrodes are expensive, but presently available cheaper alternatives also have problems. Pulse oximeters are not accurate indicators of normal or high Pa_{O_2} values, and end-tidal gas monitors are inaccurate in many patients with lung disease. Transcutaneous monitoring does reflect large changes in arterial gas tensions at all values of inspired oxygen and carbon dioxide and their sensitivity to changes in cardiac output and local capillary perfusion is clinically useful if correctly interpreted. There was little to choose between the three dual electrodes tested based on their *in vivo* performance, despite considerable differences in price and in *in vitro* response times. The current models have a limited role to play in adult anaesthetic practice, because of long initial stabilization periods, the need to resite the electrode every 4 h, and their slow response times. Future models are less likely to cause significant thermal injury, may have shorter response times, and some will incorporate two oxygen electrodes, allowing continuous use without resiting for up to 12 h [35].

ACKNOWLEDGEMENTS

We thank the subjects for their helpful co-operation in the studies, and the manufacturers for the loan of the electrodes.

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Br. J. Anaesth. (1988), **60**, 743–748

CORRESPONDENCE

HIGH FREQUENCY JET VENTILATION

Sir,—High frequency jet ventilation research has suffered because of a lack of standardization of equipment and a lack of understanding of the physical processes governing gas flow out of the jet delivery system. In the paper by Spoelstra and Tamsma [1] the authors comment on "the rectangular gas flow delivered by the HFJV unit" and, later in the paper, on "the rectangular form of the flow curve", yet their unit probably does not deliver a rectangular flow–time waveform from the jet nozzle. There are several reasons for suspecting this. In figure 2 these authors show a graph of valve setting against minute volume for duty cycles of 10–90%. At 10% duty cycle this produces an almost linear plot, but as duty cycle increases the minute volume decreases with increasing valve settings. This is attributed to an inadequate capacitor size.

I suggest that this is not the case and that the data in figure 2 describe a system where, except at low valve settings and duty cycles, there is a limitation to flow other than by the solenoid valves—probably in the gas blender and hoses. This resistance prevents full recharging of the capacitor, the effect becoming more marked when the capacitor is more completely drained per cycle, for example at high valve settings and duty cycle. Failure of full recharging results in a lower mean driving pressure in the same situations. This is shown by the authors in table I.

In turn, this implies that the flow–time waveform from the nozzle shows one that is accelerating/decelerating in form, nearer sawtooth than rectangular. Benhamou and colleagues [2] discuss this point at some length, and make the distinction between operating pressure (the pressure just before the jet lumen) and driving pressure which is measured between the gas source and solenoid valve. Had Spoelstra and Tamsma monitored operating pressure, they would have been able to make an estimate of flow waveform. The application of a rectangular voltage waveform to solenoid valves does not imply the production of a rectangular gas flow waveform.

In the same paper there also appears to be an error of interpretation. In figure 5, the authors claim that the pulmonary artery pressure waveform shows a cyclical variation with "the typical beat frequency envelope as the difference of two sine waves". This is not the case. The beat frequency envelope shows a form caused by more complex interference. From the published tracing it appears that the envelope is recurring at approx. 0.1 Hz. This is the difference between the ventilator cycles (as measured by the oesophageal and airway pressure) and alternate cardiac cycles. Close examination of the pulmonary artery pressure waveform shows alternate high and low pulse pressures. The beat frequency envelope is formed by the higher pressure cycles and the ventilator frequency; the suggestion by the authors that small changes in the phase between oesophageal and airway pressure cause the effect is not correct. Whatever the cause of the alternating pulmonary artery pressure, it does cast some doubts on the validity of the cardiac output measurement.

Finally, the authors use an $F\text{I}_{O_2}$ of 0.3 down the jet, but do not use any bias flow of gas, so any gas entrained by the jet is room air. As the true entrainment ratio is nearly impossible to determine, the actual $F\text{I}_{O_2}$ delivered to the animal is somewhere between 0.3 and 0.21. In this situation meaningful interpretation of Pa_{O_2} is difficult.

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Sir,—We thank you for providing us with the opportunity of replying to Dr Young's letter.

The suggestion that our comment on the rectangular gas flow delivered by the HFV unit may not be true is understandable, but not correct. We did actually measure the flow distal to the jet nozzle with a Fleisch type 1 flow transducer connected to a Statham differential pressure transducer (PM15ETC). The pressure transducer was first tested with the step response method. The recorded output response showed a typical second order behaviour, with an overshoot of 10%, a damping factor of 0.6 and a rise time of 10 ms. The bandwidth of the pressure transducer system, estimated from the step response, is then 35 Hz (3 dB point). Step response testing of the complete pneumotachometer system showed the same characteristics as the step response to the pressure transducer, resulting in a bandwidth of 35 Hz for the complete system.

In our experimental model the jet insufflation channel of the Hi-Lo jet tube was connected directly with the output nozzle of the solenoid valves.

Figure 1 shows the results of the flow measurements with the system described distal to the jet nozzle, but without the afterload of the dog's lung. Flow against time is rectangular for 1, 2 and 4 Hz. For 8 Hz the inspiratory time allocated to this ventilator setting coincides in such a way with rise time and overshoot of the measuring system, that no period of constant flow is recorded.

Dr Young further states that our suggestion about the cause of the non-linearity of the minute volume plots in figure 2 of our paper is not true. We think that his suggestion, limitation of flow to recharge the capacitor, is more appropriate, but this does not exclude the additional possibility that the size of the capacitor may be inadequate.

Concerning the interference of different waves as shown in figure 5 of our paper, Dr Young implies an error of interpretation. What he pointed out in his remark "the beat frequency envelope shows a form caused by more complex interference" is what we tried to reflect in our sentence

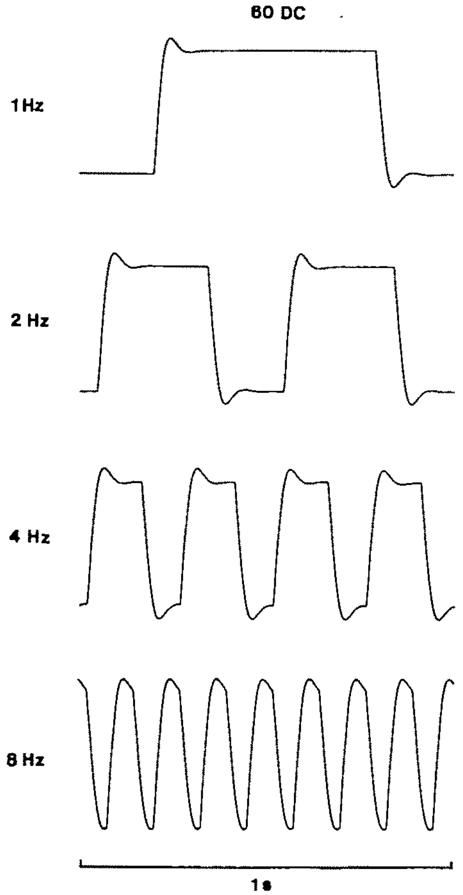

FIG. 1. Results of the flow measurements with the system described.

"Maxima and minima in PAP occur periodically because of small variations in the phase of interference of the two waves". Unfortunately, it was not clear from our text that we were considering two waves, on the one hand pulmonary artery pressure and, on the other, airway and oesophageal pressure. As this figure shows, there is no change in phase between airway and oesophageal pressure.

Flow modulation in the pulmonary circulation occurs during artificial ventilation and this interferes with indicator dilution methods of cardiac output estimation. The size of the flow modulation is related to the size of the intrathoracic pressure swings. Originally we chose to make cardiac output measurements during IPPV at a fixed point of the ventilator cycle. As injection of the indicator took place over 1.5–2.0 s, this extended over more than one ventilatory cycle during HFJV and precluded choice of a fixed cycle point for injection of the indicator. The small range in variation of cardiac output estimations during a specific setting of HFJV during our experiments suggested an averaging effect on the cardiac output estimations. As the recorded pressure swings during HFJV were small in comparison with those during IPPV, we think that this averaging effect leads to an acceptable estimation of cardiac output.

Finally, Dr Young is doubtful regarding the interpretation of Pa_{O_2}. From the results presented, it is not immediately obvious that entrainment does not play a significant role in this respect. However, in a separate study we investigated entrainment, and the results showed the entrainment volumes to be too small to influence the FI_{O_2} at the level of the distally located jet nozzle in our experimental setting. This was confirmed in studies conducted with HFJV in a lung model where FI_{O_2} was measured below the level of the tip of the jet tracheal tube by means of a mass spectrometer. In our opinion, therefore, Pa_{O_2} is influenced more by the amount of fresh gas entering the lungs than by a change in FI_{O_2} resulting from entrainment. When gas entrains, fresh gas penetrates deeper into the airways, giving rise to a change in Pa_{O_2} and Pa_{CO_2}.

A. J. G. Spoelstra
T. J. A. Tamsma
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SODIUM THIOSULPHATE DECREASES BLOOD CYANIDE CONCENTRATION FOLLOWING SODIUM NITROPRUSSIDE

Sir,—We read with interest the article by Drs Cole and Vesey [1] concerning the use of "a small bolus injection" of up to 1.5 g of sodium thiosulphate to detoxify sodium nitroprusside (SNP). The authors have demonstrated in their well controlled study that thiosulphate reduces plasma and red cell cyanide concentrations following infusion of SNP in man. In the authors' rather didactic discussion, they present a very useful clinical regimen for suspected SNP overdose which should benefit clinicians who have not encountered this problem previously or who have not used SNP to control hypertension or bleeding before this time and are now faced with this situation.

Although Drs Vesey and Cole have contributed much information on the use of SNP for the control of hypertension or to induce hypotension, we feel that other authors have also contributed valuable knowledge and deserve mention. Previous authors have shown that thiosulphate detoxifies cyanide in dogs [2–4] and studies on the metabolism of thiosulphate in dogs [5] and in man [6] have demonstrated that injected thiosulphate is rapidly excreted.

Using this information, studies have demonstrated that cyanide toxicity may be prevented in dogs [7] and in man [8] during SNP infusions. In cases of suspected cyanide toxicity, Patel and colleagues [9] treated patients (who were asymptomatic for metabolic acidosis) with bolus injections of thiosulphate. No patient in Patel's group received more than 2.5 μg kg^{-1} min^{-1} of SNP, which is much less than the safe limit of 4 μg kg^{-1} min^{-1} recommended by Drs Vesey and Cole [10]. Nevertheless, in these patients, blood cyanide concentrations were in the toxic range before administration of thiosulphate, and three of seven patients died. These authors concluded that SNP may not be the drug of choice for long-term arterial pressure control in critically ill patients with reduced detoxifying capacity. We realize that these studies were reported on the other side of the Atlantic and a "language barrier" may exist, but these reports deserve mention by the authors.

A. D. Ivankovich
B. Braverman
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Sir,—We are grateful to Drs Ivankovich and Braverman for drawing attention to the work of other authors on the subject of our paper [1] and, in particular, to the important contribution they themselves have made to our understanding of thiosulphate pharmacokinetics and cyanide antagonism. We are not aware of any "language barrier" between us, but would point out that our report was not meant to be a comprehensive review of the subject and, moreover, in our desire for brevity in a "didactic" paper, we deliberately kept references to a minimum. However, our previous thiosulphate study in dogs, which we listed, contained a fuller bibliography and covered most of the relevant studies for those who were interested.

With regard to their second point, we would emphasize that our suggested dose rate limit, of SNP 4 $\mu g\ kg^{-1}\ min^{-1}$ for long-term infusions [2] is not sacred; we expected that, with accumulating clinical experience, our suggestion would soon be modified, although how much lower these limits could be set without severely curtailing the clinical use of the drug, is a matter for debate. We would take this opportunity, however, to express a word or two of caution. Cyanogenesis by SNP is an emotive issue and there is always a temptation to ascribe unexplained deterioration of an infused patient to "cyanide toxicity" without adequate evidence.

An example may be the paper of Patel and colleagues [3]. No doubt a minority of very sick patients, particularly if malnourished or suffering from metabolic derangement, are more sensitive to the cyanide arising from SNP. However, in our opinion, the conclusions of Patel are not convincing, since:

(1) The seven out of 292 patients whose deterioration was attributed to cyanide toxicity, in the absence of the classical signs, were all older than 60 yr, and had had four or more coronary grafts and were suffering a variety of confounding complications.

(2) The suggestion that cyanide detoxication was impaired in these patients is not in accord with the plasma thiocyanate concentrations quoted, which are those normally to be expected from the doses of SNP infused [2].

(3) An undocumented statement that blood concentrations of cyanide greater than 500 μg litre^{-1} are toxic, and that all seven patients had blood concentrations in excess of this, accounting for their deterioration, suggests circular reasoning.

(4) We doubt the accuracy of cyanide measurements performed on whole blood. In the first of two cases Patel and colleagues describe in detail [3], we have the perplexing finding that, after 3 days of infusion, when the SNP was discontinued because of the patient's deterioration, a blood cyanide concentration of 585 μg litre^{-1} was recorded but, in spite of doses of thiosulphate 12.5 g and 6.25 g 6 h apart on day 3 and the subsequent improvement of the patient's condition, the blood cyanide concentration on day 4 had increased to 800 μg litre^{-1}. Even on day 5, the patient had a blood cyanide concentration of 300 μg litre^{-1}. This anomalous variation and slow reduction in cyanide concentrations, particularly following thiosulphate infusion, contrasts with the mean half-life of blood cyanide of 10 min.

The most likely reason for these dubious cyanide values is one which we have stressed previously [4–6] *viz*. the artefactual formation of cyanide on assay. The conventional method for cyanide measurement involves initial acidification of the blood sample, before the isolation and concentration of the cyanide. With whole blood, it has been shown that this results in the formation of cyanide from thiocyanate by oxyhaemoglobin, and the amount so generated is related to the plasma thiocyanate concentration [7]. Thus where thiocyanate concentration is high, as it is in patients receiving infusions of SNP lasting several days (and if they are smokers it may be even higher [2]) there is considerable error in the quoted values of whole blood cyanide. We again suggest that the valid basis on which to assess possible cyanide toxicity is the measurement of the cyanide concentration of *plasma* from freshly drawn blood, particularly since 98% of the blood cyanide is sequestered in the red cell [6, 8].

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C. J. Vesey
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ESSENTIAL MONITORING

Sir,—Professor Sykes, in his article on Essential Monitoring [1] drew attention to the need for expired volume *and* airway pressure monitoring as a check on ventilator function. Recently, we discovered a potential hazard of expired volume monitoring that, to our knowledge, has not been described before.

During clinical evaluation of a prototype airway pressure failure alarm, trial disconnections were made at various places in a circuit comprising a Blease Manley 4 ventilator, operating as a minute volume divider and a Medishield Wright's respirometer at the expiratory port. A Medishield AGS scavenging system was connected to the ventilator. Following a complete disconnection at the tracheal tube (which was detected by the pressure failure alarm) it was noticed that the respirometer was still recording 500-ml "breaths" during the expiratory phase of the ventilator.

It was found that the scavenging system was aspirating room air through the Wright's respirometer via the open expiratory limb of the circuit. As this occurred only when the ventilator expiratory valve was open, the respirometer behaved exactly as if measuring the patient's expired gas.

The message is that end-tidal carbon dioxide monitoring may be more expensive than simple ventilator alarms, but will detect failure of ventilation in every case.

M. J. Jordan
London

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Sir,—Thank your for allowing me to comment on the interesting letter from Dr Jordan. The whole thrust of my article was to try and indicate how conventional monitoring systems could fail to detect malfunction if they were not integrated completely into a comprehensive system. I pointed out that it was necessary to use both end-tidal carbon dioxide monitoring *and* expired volume monitoring to detect rebreathing during both spontaneous and controlled ventilation, and I am delighted that Dr Jordan has identified a further problem with expired volume monitoring.

Your readers might be interested to know of another source of error which I encountered some years ago. In the early models of the Manley Pulmovent, there was an excessively large gap between the expiratory valve and its seating, so that approximately equal volumes of gas passed through the valve during inspiration and expiration. The interruption of flow between these two phases of respiration was inadequate to reset an electronic Wright's Respirometer, so that the tidal volume displayed appeared to be appropriate for the ventilatory rate and the minute volume set on the flowmeters. However, the patient's chest movement was less than would have been expected. Replacement of the electronic respirometer by the standard mechanical model clearly demonstrated that gas was flowing through the expiratory valve during both inspiration and expiration, thus revealing the true cause of the malfunction.

I hope your readers will continue to record their experiences in this field, so that other anaesthetists may be made aware of possible deficiencies in monitoring systems.

M. K. Sykes
Oxford

MORTALITY AND MORBIDITY AFTER HIP FRACTURE

Sir,—I wish to take issue with Davis and colleagues [1] over a point in their otherwise interesting and useful paper on mortality and morbidity after hip fracture. They devote utterly disproportionate space in their summary to the statement "A delay to surgery of more than 24 h from admission was also associated with an increased 28-day mortality."

The *only* support for this statement is in their table VI, where surgical delay is listed as an association with *long-term* mortality. This appears to have been identified by univariate analysis, and there is no discussion of considerations such as that patients in whom surgery was delayed may have been in such poor condition as to justify the delay. It may then be argued that the delay was not long enough to permit adequate resuscitation.

The matter is mentioned briefly in the discussion, and the work of Aldrete, Hamilton and Hingson [2] is quoted in support. This is a misrepresentation. Aldrete demonstrated a possible adverse effect only when a delay of more than 48 h was compared with one of 13–48 h; patients who had a delay of less than 12 h did worst of all. The only support for an adverse effect of delay is on morbidity, from the work of Villar, Allen and Barnes [3]. These authors noted a poorer psycho-social recovery in patients whose surgery had been delayed, but their study was limited to the 145 preoperatively healthy patients of their original group of 205. Other major papers show either no difference with delay [4,5] or a difference only after a delay of over 48 h [3,6,7].

Statements made in summaries are likely to be the most influential. In this case the effect could be extremely harmful to those patients who need time for adequate assessment and resuscitation before surgery; there remains no evidence for anything but harm if the operation is performed within 12 h of injury.

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Sir,—Thank you for the opportunity of replying to the letter from Dr Dodds. My comments in reply are as follows.

Dr Dodds' letter correctly raises the very important issue of adequate preparation for anaesthesia and surgery in elderly patients with hip fracture. A delay of longer than 1 day from injury to surgery *was associated with* increased mortality generally in our study and should have appeared in both columns of table VI. This association, however, does not imply a *cause and effect* relationship. The assumption that it is the patients in poorer shape in whom surgery tends to be delayed may or may not be true, however, as many other factors come into play, such as lack of theatre time or staff, and the generally low priority of these unfortunate people in the "pecking order" for hospital facilities. In many hospitals there is a somewhat fatalistic approach to their surgical care which is often placed into the hands of inexperienced and unsupervised junior doctors, to be done as soon as possible as "an acute". Conversely, unnecessary delays to surgery sometimes result from an over cautious approach to anaesthetic assessment.

The limitations of space prevented discussion of issues peripheral to the central theme of the anaesthetic contribution to mortality. Nevertheless, we totally agree with Dr Dodds that appropriate time for adequate assessment and resuscitation MUST be allowed before surgery. Surgery for fractured hip in the elderly is an *urgent*, but not an *emergency* procedure.

F. M. DAVIS
Christchurch, New Zealand

GENERAL ANAESTHESIA FOR CAESAREAN SECTION

Sir,—The study reported by Drs Dann, Hutchinson and Cartwright [1] showed that pretreatment with alfentanil attenuated the haemodynamic response to intubation in patients undergoing elective Caesarean section. Unfortunately, the study was marred by the use of an anaesthetic technique (nitrous oxide, oxygen and an opioid) known to be associated with an unacceptably high incidence (10–20%) of maternal awareness. Indeed the incidence of awareness in this study was 11%. In the majority of cases of awareness dealt with by the Medical Defence Union a nitrous oxide, oxygen and opioid technique had been used [2]. The addition of 0.5% halothane, 1% enflurane or 0.75% isoflurane has been shown to prevent maternal awareness during general anaesthesia for Caesarean section, without adverse effects on the neonate [3,4].

When obtaining informed consent, the authors "stressed that there was a small risk of awareness". Perhaps if patients had read the harrowing account of awareness during Caesarean section, published in this journal a few years ago [5], that consent would not have been forthcoming.

J. G. JENKINS
Guildford

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Sir,—Thank you for giving us this chance to reply to Dr Jenkins' letter. It is hard to understand why he considers that the study was marred by the anaesthetic technique used.

In suggesting the administration of an opioid before delivery of the infant, we are breaking new ground in obstetric anaesthesia, and we feel that it is vital that our observations are made in as simple a model as possible. As obstetric anaesthetists we are continually mindful of the problem of awareness, but we, our patients, and the District Ethics Committee all agreed that in this study it was reasonable to proceed without a volatile agent.

We are proceeding with further studies using alfentanil, this time in conjunction with 0.5% halothane, and this will allow us to separate the effects of the opioid and the volatile agent. It is a pity that this step-wise approach has not been used more often, as many studies present too many variables to allow proper analysis of the findings.

W. L. DANN
A. HUTCHINSON
D. P. CARTWRIGHT
Derby

DIAGNOSTIC TEST FOR HALOTHANE HEPATITIS

Sir,—Kenna and colleagues [1] described a diagnostic test for halothane associated hepatitis in patients with liver failure. Is this test any better than the numerous others which have been described to make this diagnosis, but which have failed to achieve common usage?

The macrophage migration inhibition test [2] and the lymphocyte stimulation test [3] were proposed for the diagnosis of halothane associated hepatitis almost 20 years ago. A skin test using conjugated halothane was suggested by Carney and Van Dyke in 1972 [4], a positive reaction in 24 h indicating a delayed hypersensitivity response. A test investigating the viability of lymphocytes when exposed to a phenytoin biotransformation system generating phenytoin epoxides was described in 1985 [5].

Auto-immune complex fixation, smooth muscle, liver-kidney microsomal, anti-thyroid and anti-mitochondrial autoantibodies have all been proposed to support a diagnosis of halothane associated hepatitis [6]. A later study [7] demonstrated that circulating autoantibodies were as common in patients with viral induced liver failure as in patients with liver failure after halothane.

In patients with halothane associated hepatitis, antibodies to the surface of halothane altered rabbit hepatocytes were first reported by the Kings College Hospital Group in 1980 [8]. In the ensuing 7 years the usefulness of this test in diagnosing halothane associated hepatitis has not been confirmed by any other centre. The test requires independent validation before it can be accepted.

In the discussion section Kenna and colleagues [1] implied that unexplained postoperative pyrexia, nausea, vomiting and malaise after halothane are contraindications to its subsequent use. As many as 60% of postoperative patients develop fever and in more than half of these the cause is unexplained [4]. Fever after halothane is no more common than fever after any other volatile anaesthetic agent [9, 10]. This recommendation of the authors is, therefore, unduly restrictive.

H. Wark
Sydney

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Sir,—We thank Dr Wark for his comments on our paper and are grateful for an opportunity to reply to some of his comments.

Dr Wark is correct in suggesting that a number of tests have been developed in an attempt to diagnose halothane-associated hepatitis. The leucocyte migration inhibition test, the lymphocyte stimulation test, skin tests, lymphocyte cytotoxicity to phenytoin epoxides all require either direct access to the patient or the availability of viable lymphocytes from the patient. Demonstration of circulating antibodies specific for halothane-induced liver membrane antigen was described first using indirect immunofluorescence and antibody dependent, cell-mediated cytotoxicity. Both techniques, well validated by blocking and absorption studies, are time consuming, cumbersome and require specific expertise. To overcome these problems we developed an enzyme-linked immunosorbent assay which can be readily performed in any well-equipped laboratory. All results are consistent and have been confirmed by other methods, including immunoblotting. Furthermore, all studies have shown that the presence of these "halothane antibodies" appears to be specific for patients with halothane hepatitis, since we have not detected them in any other condition. These findings of specificity contrast with tests of immune complexes and auto-antibodies, which are neither specific nor sensitive.

The findings of halothane antibodies in serum only of patients with halothane hepatitis have been repeated by colleagues both in Dr Pohl's laboratory at the National Institutes of Health, Bethesda, U.S.A. and in Kings College Hospital. We are unaware of any report which has failed to confirm our findings.

Finally, the Committee on the Safety of Medicines in September 1986 have stated *inter alia* that "The history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contraindication to its future use in that patient" and they add further that the manufacturers of halothane have agreed with this recommendation.

J. G. Kenna
Bethesda
R. Williams
London
J. M. Neuberger
Birmingham

Br. J. Anaesth. (1988), **60**, 749–750

BOOK REVIEWS

A Synopsis of Anaesthesia, 10th Edition. By R. S. Atkinson, G. B. Rushman and J. A. Lee. Published by Wright. Pp. 898; indexed. Price £25.

This, the 10th edition of *Synopsis*, sits conspicuously upon the shelf among its predecessors, being a larger tome in height and width by a factor of almost 1.3. As a result, it may no longer be regarded as a handbook. Nonetheless, this work retains its excellent value as a source of basic, sound information and reference.

The three sections of the previous edition have been revised to six. The first section, comprising one chapter only, deals with history; the authors make no apology for this, believing that the practising anaesthetist should have an appreciation of the development of the specialty. The other sections comprise Basic Sciences (four chapters); General Anaesthesia (16 chapters) and Choice of Anaesthetic (nine chapters), which together constitute more than 50% of the book; Regional Techniques (three chapters) and Cardiorespiratory Intensive Therapy (10 short chapters).

The text, although not devoid of the short notes style of previous editions, is generally more discursive and readable than before. With a new typeface, it has a cleaner look.

Criticisms of the book include a tendency to haphazard classification of material (the inclusion of Ayre's T piece in the section on tracheal intubation), a somewhat random and illogical sequence of material (the chapter on medical disease influencing anaesthesia suffers in this way, although the reference list is impressive), a tendency to repetition (two headings of failed intubation), and the occasional error of fact (the use of mu instead of eta to designate viscosity; the incorrect dose of insulin for the Alberti regimen). In addition, it is surprising to see a recommendation to use gallamine to treat bradycardia!

The bouquets must go to the dictionary of rare diseases, the comprehensive referencing (the most recent reference is 1987 and the chapter on spinal anaesthesia contains 423 references) and the index, which appears to have been expanded in comparison with the previous edition. In addition, the account of the technique of blind nasal intubation is recommended reading. Choice of anaesthetic, once merely a chapter on the influence of the patient's condition or the type of surgery, has been upgraded to a whole section—surely the centrepiece of the book, and the area to which many trainees will refer regularly. The wide-ranging chapter on surgical operations contains no fewer than 267 references.

Remnants of dated practice remain throughout this book; for example, a whole chapter on the technique of hypothermia in anaesthesia. The chapter on accidents, complications and sequelae remains somewhat unbalanced. In the final section on critical care, the shorter chapters might be combined on occasion and the section on poisoning expanded.

On the whole this synopsis continues to provide a text on "everything you wish to know". It remains to be seen if this is still the correct format for anaesthesia, which has developed into several subspecialties with a recent proliferation of textbooks in every field. However, for the novice anaesthetist, this continues to be one of the most useful references of anaesthetic practice.

D. Fell

Lectures in Anaesthesiology 1987/2. Edited by J. S. M. Zorab and R. Weller. Published by Blackwell Scientific Publications. Pp. 108; illustrated; not indexed. Price £9.00.

This slim volume is one of a series of twice-yearly publications containing "lectures of interest to anaesthesiologists". This issue contains seven essays which are unrelated and range in subject matter from viral hepatitis to abdominal aortic aneurysm. Every article is extremely readable and is constructed at a level appropriate for a candidate undertaking the Part III F.F.A.R.C.S. examination.

In some ways this book is similar to other well-known and longer established collections of review articles. However, it differs in one major respect, in that the extent of referencing is less comprehensive. At £9 for approximately 100 pages, it is also relatively more expensive than the other regular collections of reviews in anaesthesia.

Although this booklet can be recommended as a group of interesting and enjoyable articles, it is difficult to be certain of the intended audience. We are informed from the notes on the cover that the series is designed for those anaesthetists who do not have access to regular continuing education. However, the contents of this present issue are clearly not appropriate for anaesthesia in Third World countries and there are many other sources of similar information which are readily available to those practising anaesthesia under more fortunate circumstances.

G. Smith

History of Blood Gas Analysis. International Anesthesiology Clinics, Vol 25, No. 4. Edited by J. W. Severinghaus and P. B. Astrup. Published (1987) by Little, Brown and Company, Boston. Pp. 224; illustrated; indexed. Price $24.00.

A subject can be regarded as established when its history is recorded. The past few years have seen two other accounts of the history of blood-gas analysis from the same authors. It is acknowledged in the preface that the present volume is a slightly modified and updated version of articles which originally appeared in the *Journal of Clinical Monitoring*.

Professors Severinghaus and Astrup review the development of electrochemistry and the events and characters associated with the progression to the automated blood-gas analysers used today. Scarcely 25 years have elapsed from a time when a blood-gas analysis required 30 minutes and considerable skill to perform, to a time when no skill and only a few minutes are required.

Much of the new information in this volume is found in the section on oximetry, where Professor Yoshiyuki Honda has added new detail to the history of pulse oximetry. This advance in monitoring is often seen as a U.S. invention, whereas the concept was developed in Japan but not exploited.

Those with an interest in the history of anaesthesia will find the volume fascinating in the personal details and insights of the characters involved. Whether it is worth the expense, when much of the material has been published elsewhere and is readily accessible, is open to question.

C. D. Hanning

1987 Year Book of Anaesthesia. Edited by R. D. Miller. Published by Wolfe Medical Publications Ltd. Price £37.50.

As the title suggests, the popular *Year Book of Anaesthesia* is an annual update containing a wide selection of relevant abstracts from the current literature, followed by pertinent editorial comment. The Editorial Board, comprising the five distinguished American academic anaesthetists, R. D. Miller, R. R. Kirby, G. W. Ostheimer, M. F. Roizen and R. K. Stoelting, selected those reports thought to have the most impact on the specialty of anaesthesia and its clinical practice.

The 1987 *Year Book* has the usual format, beginning with a brief introduction followed by more than 300 abstracts allocated to 15 chapters. Most relevant European Journals (with the notable exception of the *British Medical Journal*) are represented among the 83 journals cited, although less than 20 % of the abstracts chosen emanate from outside the North American continent.

Notwithstanding this transatlantic discrepancy, the chapters are well-balanced, with emphasis on subjects likely to be of interest and importance to British anaesthetists (e.g. standards of monitoring practice, the elderly patient, A.I.D.S., anaesthesia for lithotripsy). Editorial comment is, in general, constructive and stimulating.

The real value of a Year Book is to provide those with limited access to library facilities or limited time to peruse journals, with the chance to ensure they are informed on important issues, and at the same time to encourage the well-read to pursue, in more depth, those more obscure issues which may be at the periphery of the subject. The 1987 *Year Book* achieves this purpose.

At the price of £37.50, it is expensive and is intended for departmental or library purchasing lists, on which it should command high priority.

D. A. B. Turner

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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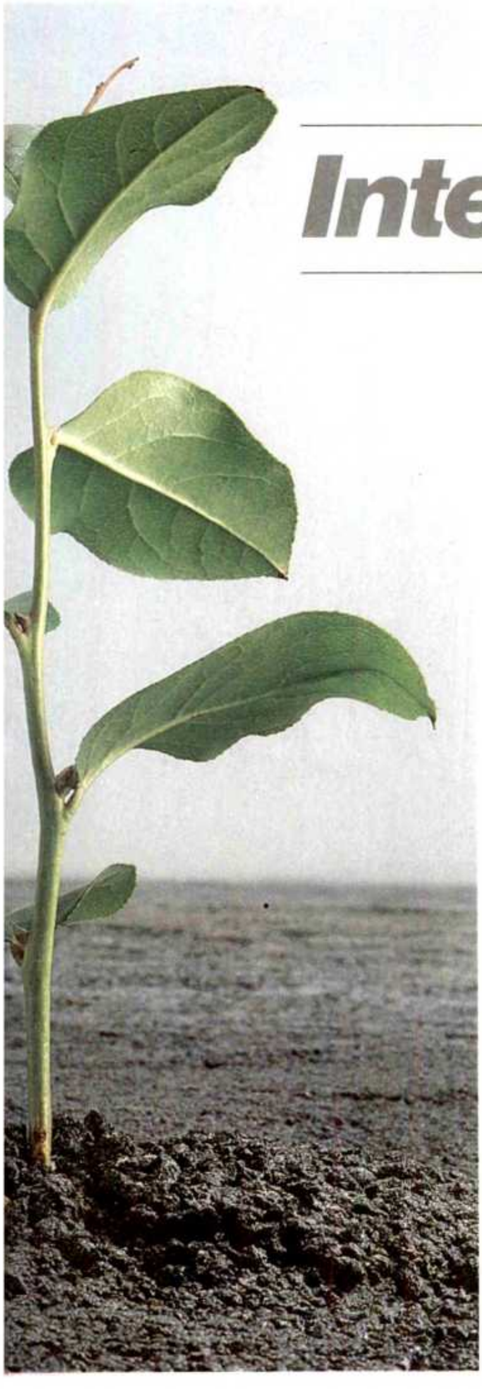

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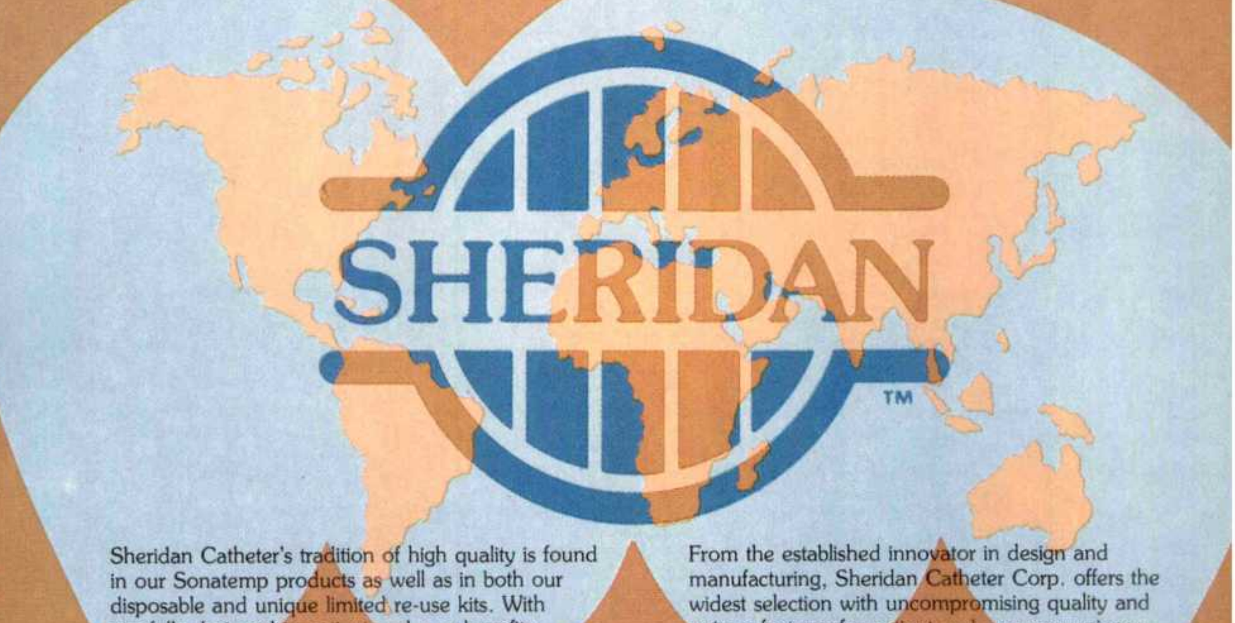

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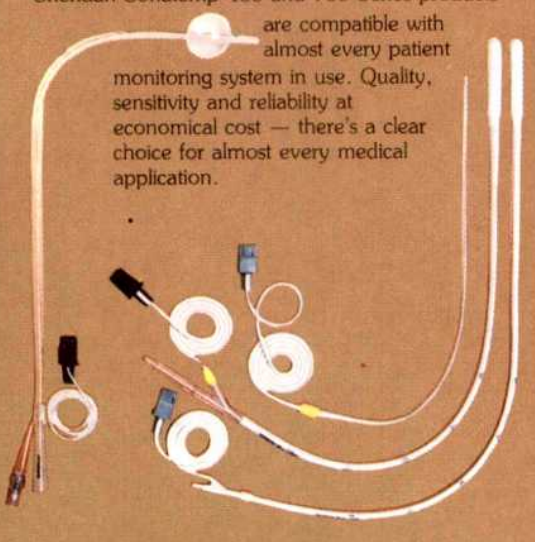

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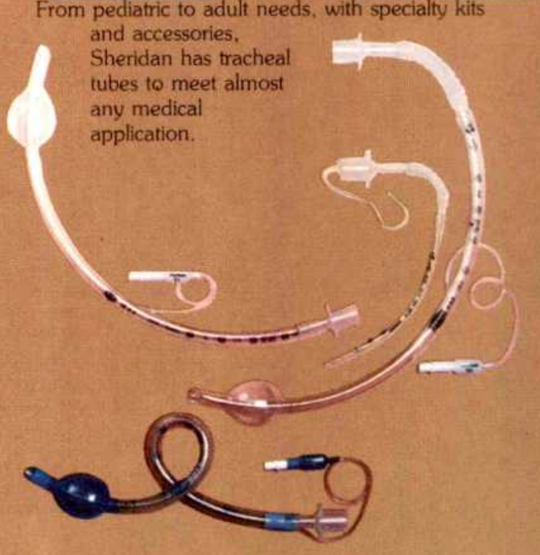

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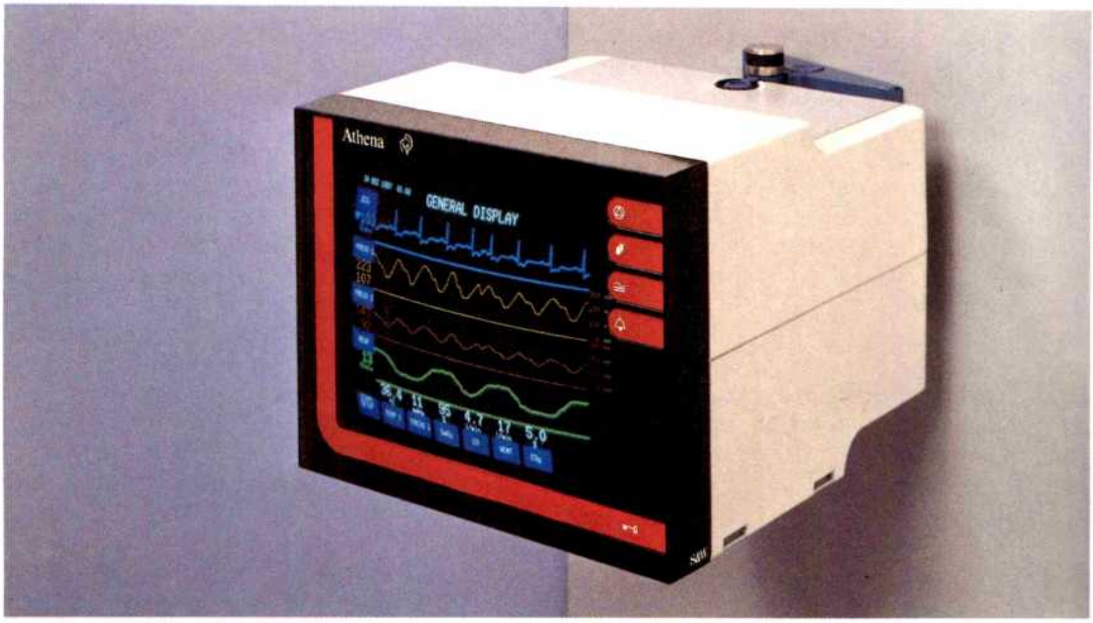

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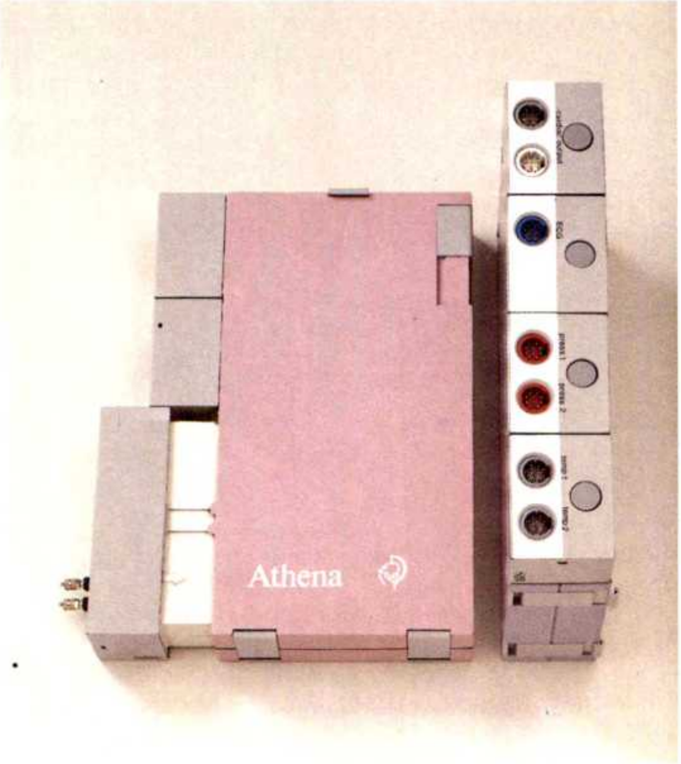

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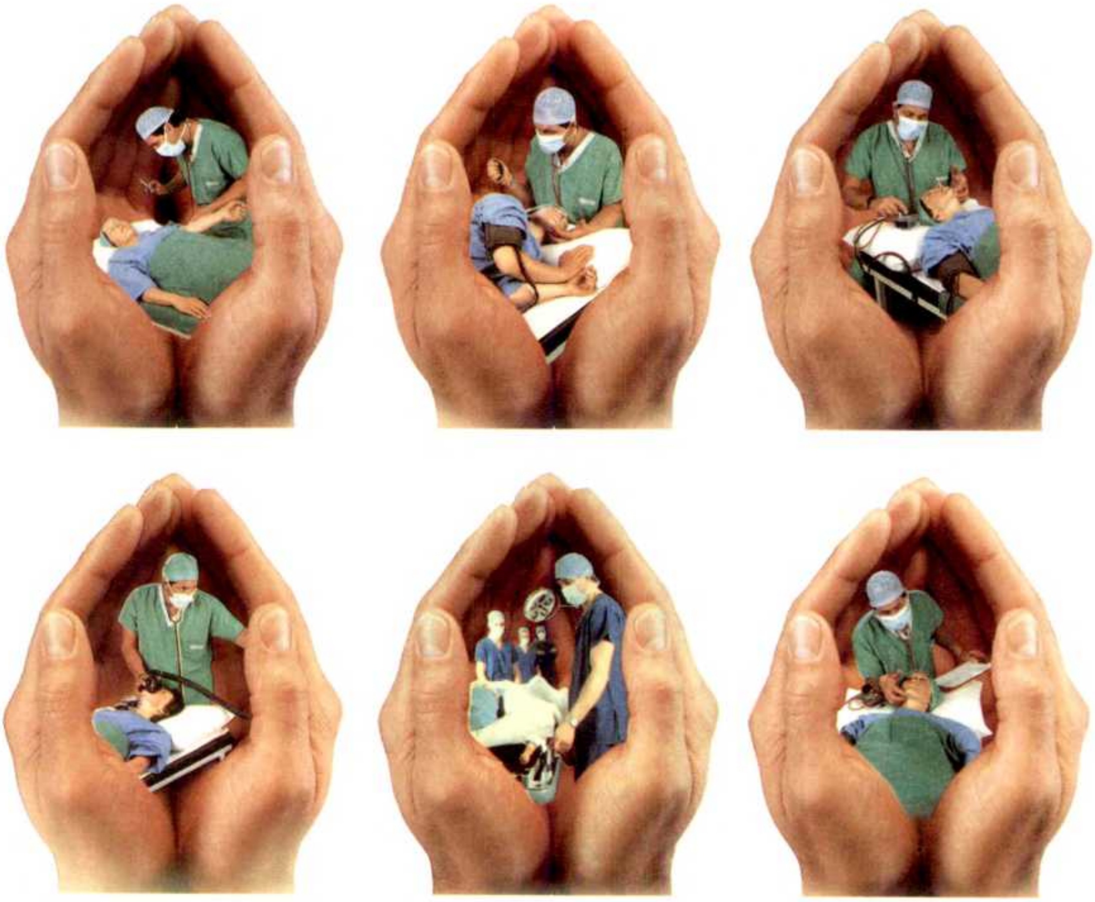

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EDITORIAL

THE LESSONS OF CEPOD

The publication of the results of the Confidential Enquiry into Perioperative Deaths (CEPOD) by the Associations of Anaesthetists and of Surgeons [1] is an important landmark in audit in the two disciplines. The enquiry set out to review all deaths within 30 days of a surgical operation in three geographical areas of England. In each case a local reporter notified relevant deaths to the CEPOD office and the consultant surgeon and anaesthetist involved received questionnaires. The responses were reviewed by assessors from anaesthesia and the appropriate surgical specialty. The information sought for assessment was detailed, requiring careful access to the patient's records. The assessors were asked to indicate their opinion as to the cause of death, avoidable elements, departures from ideal practice, if they would have become involved in the case under similar circumstances and whether or not the patient should have received any surgical operation in any centre.

The assessors were invited to judge if the death was attributable, wholly or partially, to anaesthesia or surgery and to comment on the choice of operation or management, the grade of surgeon, any failure of organization or equipment or failure to apply knowledge or appropriate care, experience or supervision. Other factors considered were drug effect and disease, and fatigue and physical or mental impairment on the part of the doctor.

It was possible to analyse 4034 deaths, estimated to be about 80 % of deaths that might have been reported. The total number of surgical operations in the regions for the period of the study is calculated to have been 485 850. Thus the crude 30-day death rate was 0.8–1.0 %.

Seventy-nine percent of CEPOD deaths were in patients older than 65 years of age. The commonest working diagnoses for all the patients were fractured femur, intestinal obstruction, aortic aneurysm, peptic ulcer and cancer of the colon; these categories accounted for 34.2 % of the total. The commonest clinical causes of death were bronchopneumonia (13.5 %), congestive cardiac failure (10.8 %), myocardial infarction (8.4 %), pulmonary embolism (7.8 %) and respiratory failure (6.5 %).

The responding surgeons admitted that, at times, there were deficiencies in preoperative management, technical difficulties or misadventure and inadequacy of notes for the purposes of this audit.

The surgical assessors considered that surgery had contributed totally or partially to the death in 30 % of the patients. In one-third of these there was a failure in preoperative management and in one-fifth it was considered that the grade of the surgeon was inappropriate. In 22.2 % of all deaths, avoidable elements might have reduced the chances of death and in 6.5 % it was considered that no operation should have been undertaken at all. They considered that anaesthesia had contributed to the death in 1.8 % of the patients.

It was considered that the progression of the presenting disease had contributed to death in 67.5 % of all the patients, with progress of an intercurrent disease (presumably not the cause of operation) being relevant in 44.3 %. These last two values are very close to a similar analysis by the anaesthetic assessors.

Anaesthesia was regarded as the sole cause of death in only three individuals (0.1 %), although it was considered to have played some part in a total of 410 deaths. "Failure to apply knowledge" was noted in 75 % of cases. Lack of care, of experience or knowledge, and failure of organization were the other leading factors.

For all the CEPOD deaths, it is interesting to examine the distribution of trainees at the senior house officer or registrar grade as the most senior anaesthetist present. These doctors undertook 32 % of cases during normal working hours, but 54 % outside normal hours. Consultants had been asked for advice in only 21 % of cases in which a junior anaesthetist was involved.

In 13.9% of cases the anaesthetist was not satisfied with the preparation of the patient for operation and in 4.3% of the patients cardiac arrest occurred during the administration of the anaesthetic, although these subjects were not necessarily those which the anaesthetists regarded as poorly prepared.

In 10.6% of CEPOD deaths the anaesthetic assessor would have refused to anaesthetize the patient.

Considering those cases in which the anaesthetic assessor considered that there had been an avoidable element of anaesthetic practice contributing to the death, analysis with respect to grade of anaesthetist as a factor showed that criticism attached to consultant anaesthetists and to senior house officers and registrars with roughly comparable frequency (between 20 and 35%). In the case of senior registrars' practice, the criticism was levelled much less frequently.

The CEPOD enquiry is the first in which there has been a joint audit of anaesthetic and surgical practice. Although surgeons contributed greatly to the Association of Anaesthetists' enquiry [2] in 1979, that audit was directed solely at anaesthetic practice. The successful conclusion of an elaborate study of this kind is a tribute to those who conceived and executed the plan and prepared the report, and also to the clinicians and assessors who, in spite of some initial refusers and later losses, stayed loyal to the study to the end. The fact that the results do not reveal a totally rosy picture should be taken as a challenge and not a cause for despondency. Most anaesthetists and surgeons feel intuitively that, with the passage of time, the quality of practice in their discipline is becoming better and safer.

Nevertheless, there are important lessons and conclusions. The good news is that the role of anaesthesia in surgical death appears to be commendably small. That is in keeping with the 1979 U.K. study and accords with a recent report from New South Wales [3]. The fact that so few people die as a consequence of anaesthetic procedures raises the question as to the need for elaborate and expensive participation of the specialty of anaesthesia in mortality (as opposed, perhaps, to morbidity) audit. It should be remembered, however, that the quality of surgical audit would be greatly impaired without anaesthetic participation and that, in any case, the boundary between anaesthetic practice and surgical practice may not be too easy to draw. If it is remembered that the common stated causes of death in surgical patients in the CEPOD study can all be classified as cardiorespiratory problems, the data may point to the need for much more intense study of the postoperative period to determine how much of this is preventable with greater collaboration between the disciplines.

No-one can take comfort from the fact that so many patients who died after operation had been denied the services of fully trained specialist anaesthetists, and it is perhaps equally alarming that consultants responsible for the practice of junior colleagues seem to be so rarely aware that patients who were destined to die were undergoing treatment at all. When this is coupled with the fact that there is still a considerable proportion of cases in which correct preparation and correct consultation between members of the team has not occurred (a matter aired in the 1979 study [2]), the anxiety becomes all the greater. At a time when discussions are taking place in the United Kingdom on the whole structure of anaesthetic staffing, with strong implications for a rationalization of the delivery of emergency services [4], the CEPOD data are particularly pertinent. Everyone knows that there is a great deal of operative intervention conducted out of hours, and often not in the best possible manner, when the need of the patient is by no means as urgent as the timing implies. This in itself merits careful analysis because it would not be surprising to learn that such practices increase morbidity, if not mortality.

Perhaps the greatest contribution of CEPOD in the United Kingdom is that it is likely to promote a greater acceptance of audit in future. Any doctor perusing the CEPOD report, which is very readable, will be impressed by the broad indicators that emerge from an enquiry of this kind and must surely be interested in how he or she compares with the performance of others.

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PHARMACOKINETICS OF ALFENTANIL IN TOTAL I.V. ANAESTHESIA†

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SUMMARY

Alfentanil was administered, together with midazolam, as part of a total i.v. anaesthetic technique. The pharmacokinetics of alfentanil were determined in 10 female patients undergoing lower abdominal surgery. The dose regimen of alfentanil, based on simulation studies, consisted of a two-stage infusion following an initial bolus dose. The kinetics of alfentanil were described by a linear two-compartment open model. The total plasma clearance ranged between 93 and 431 ml min^{-1} *(mean 249 ml* min^{-1}*). The apparent volume of distribution at steady-state ranged between 0.27 and 0.64 litre* kg^{-1} *(mean 0.44 litre* kg^{-1}*). The apparent volume of distribution (*Vd^{β}*) was 0.58 litre* kg^{-1}*, resulting in a terminal half-life of 112 min. Alfentanil concentrations at the time of extubation and postoperative analgesic requirements were also monitored. Good correlation between respiratory depression and plasma alfentanil concentration was found. Neither lower abdominal surgery nor the simultaneous administration of midazolam seemed to affect the kinetics of alfentanil as compared with results from studies in healthy volunteers. The short half-life of alfentanil, resulting from a small volume of distribution, makes it suitable as part of a total i.v. technique. Consideration must be paid, however, to interindividual differences in the pharmacodynamic response and in plasma clearance.*

Increasing awareness of the toxic and metabolic problems associated with the use of nitrous oxide [1–3] has led to a greater interest in the technique of total i.v. anaesthesia. The present report describes the use of midazolam and alfentanil in such a technique. Alfentanil is an analgesic which offers a rapid onset of action as well as haemodynamic stability. In addition, it has a short elimination half-life [4, 5]. If alfentanil is to be included in a total i.v. technique, knowledge of its pharmacokinetics, and of its interactions with other drugs during anaesthesia, is of fundamental importance for its rational and safe use. The aims of the present investigation were: to construct a dose regimen based on simulation studies which may be used to provide analgesia during surgery; to determine the pharmacokinetics of alfentanil during major surgery; and to compare the simulated and the observed plasma concentration–time profiles.

PATIENTS, MATERIAL AND METHODS

Patients

Ten female patients, undergoing elective abdominal hysterectomy, participated in the study. Their ages varied between 36 and 53 yr and their body weights between 53 and 88 kg (table I).

The study was approved by the Ethics Committee of the Medical Faculty of Uppsala University; informed consent was obtained from each patient.

Premedication and anaesthetic procedure

Pethidine 75 mg and atropine 0.5 mg were given i.m. as premedication 30 min before the induction of anaesthesia. Anaesthesia was induced with bolus doses of alfentanil and midazolam and maintained with infusions of these drugs.

Alfentanil was administered as an initial bolus

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TABLE I. *Body weight, total infusion time, total dose of alfentanil and area under the concentration–time curve (AUC) in 10 female surgical patients*

Patient No.	Weight (kg)	Duration of infusion (min)	Total dose (mg)	AUC (mg min litre^{-1})
1	53	75	11.2	28.6
2	66	90	15.1	52.9
3	81	75	17.2	39.9
4	88	75	18.7	94.3
5	64	75	13.6	48.3
6	66	75	14.0	70.6
7	65	75	13.8	48.9
8	67	75	14.2	99.0
9	76	75	16.2	173.2
10	56	75	11.9	65.2

dose of 75 μg kg^{-1} in combination with a two-stage infusion consisting of 5 μg kg^{-1} min^{-1} for 15 min followed by 1.0 μg kg^{-1} min^{-1} until closure of the abdomen commenced. The total duration of alfentanil infusion corresponded to doses of 11.2–18.7 mg, with a mean dose of 14.6 mg (table I).

Midazolam was given as an initial bolus dose of 300 or 250 μg kg^{-1} (patients Nos 1–5 and 6–10, respectively) followed by a two-stage infusion consisting of 11 μg kg^{-1} min^{-1} for 15 min and 2.1 μg kg^{-1} min^{-1} for as long as the alfentanil infusion was maintained.

Neuromuscular blockade was achieved with pancuronium in all patients, and artificial ventilation (end-tidal carbon dioxide = $4.0 \pm 0.2\,\%$) with oxygen in air ($F_{I_{O_2}} = 0.3$) was provided during anaesthesia. At the end of surgery, neuromuscular blockade was antagonized with neostigmine 2.5 mg plus atropine 1.0 mg.

Blood sampling and assay

Blood samples were collected from a peripheral vein before and at 2, 5, 10 and 15 min after the start of the infusion regimen, and then every 15 min until the infusion was terminated. After the infusion, samples were drawn at 2, 5, 10, 15, 30 and 60 min and then every 1 h for 6 h. The plasma was separated and stored at −20 °C until assayed. Plasma concentrations of alfentanil were determined with a specific radioimmunoassay with a claimed sensitivity of 50 pg and intra- and interindividual assay variations of 3.7 and 3.3 %, respectively [6].

Postoperative observation

Before extubation of the trachea, ventilation was reduced gradually to give an end-tidal carbon dioxide concentration of at least 6 %. If spontaneous ventilation did not return, naloxone 0.1 mg was given i.v. The length of time between the end of the infusion of alfentanil and the first postoperative analgesic dose of ketobemidone was recorded.

TABLE II. *Mean alfentanil pharmacokinetic values used for the simulation in five patients scheduled for elective surgery under general anaesthesia [5]*

Total plasma clearance (ml min^{-1})	235
Apparent volume of distribution (litre kg^{-1})	0.44
Elimination half-life (min)	87

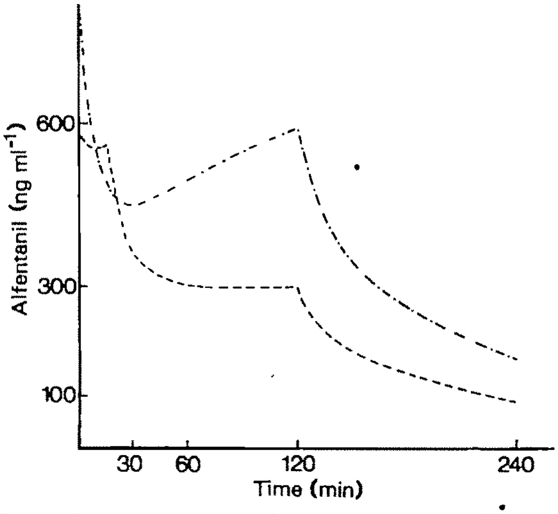

FIG. 1. Simulated concentration–time profiles for alfentanil, for the dose regimen used in the present study (- - -) and the dose regimen used by Fragen and colleagues [5] (-··-).

Design of alfentanil infusion regimen

It was intended that the infusion of alfentanil should give a steady-state concentration of about 300 ng ml^{-1}, which has been found to be satisfactory in patients ventilated with nitrous oxide [4]. The infusion regimen was constructed after numerous simulation studies based on published pharmacokinetic data (table II). The resulting concentration–time profile is shown in figure 1, together with the simulated profile for the dose regimen used by Fragen and colleagues [5]. Simulations were performed with the aid of the simulation program DARE-P [7]. The maintenance infusion was calculated from the equation [8]:

$$k_0 = Cl \cdot C^{ss} \qquad (1)$$

where k_0 is the maintenance infusion rate, Cl the total plasma clearance and C^{ss} the desired steady-state plasma concentration.

Compartmental pharmacokinetic analysis

For fitting of a two-compartment open model to the observed individual plasma concentration–time data, the non-linear least square regression program DARE-MINUIT (University of Uppsala, Sweden) was used. The data points were weighted as equal or $1/y$ (y = plasma concentration value) to obtain the best fit. On the basis of the obtained estimates of the micro-rate constants k_{10}, k_{12} and k_{21}, the following equations were used to calculate the disposition rate constants (α and β) and the apparent volume of distribution (Vd^{β}).

$$k_{10} = \frac{\alpha \cdot \beta}{k_{21}} \qquad (2)$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10} \qquad (3)$$

$$Vd^{\beta} = \frac{Cl}{\beta} \qquad (4)$$

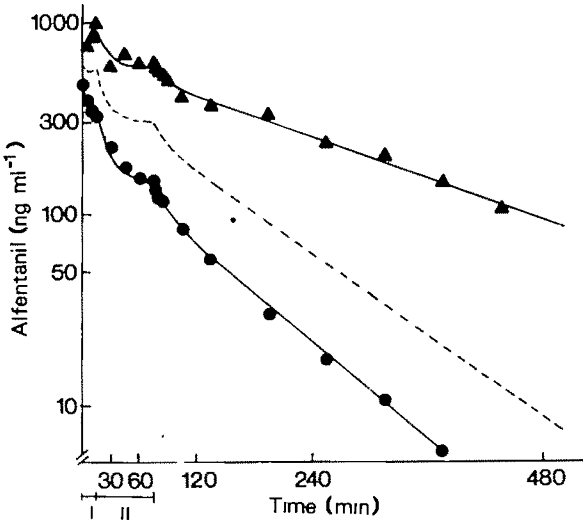

FIG. 2. The concentration–time profiles for the two patients with the lowest (●) and highest (▲) steady-state concentrations. The solid lines show the fit and the broken line the simulated concentrations. I and II represent the durations of the first and second infusions, respectively.

Non-compartmental pharmacokinetic analysis

Based on the compartment-independent approaches, the total plasma clearance (Cl) and the apparent volume of distribution at steady-state (Vd^{ss}) were calculated from the following equations [9]:

$$Cl = \frac{\text{Total dose}}{\text{AUC}} \qquad (5)$$

$$Vd^{ss} = \frac{\text{Total dose} \cdot \text{AUMC}}{\text{AUC}^2} - \frac{(A \cdot T^1 + B \cdot T^1 \cdot 2 + B \cdot T^2)}{2 \cdot \text{AUC}} \qquad (6)$$

where T^1 and T^2 are the infusion times and A and B are the infused doses during the infusions at the first and second rates, respectively. The area under the concentration–time curve (AUC) and the area under the curve of the product of time and drug concentration (AUMC) for the individual curves were calculated with the linear trapezoid rule up to the last data point. The extrapolated area to infinite time for AUC and AUMC beyond the last data point was estimated by integration [9].

RESULTS

The dose regimen for alfentanil resulted in a mean (±SD) plasma concentration of 291±132 ng ml^{-1} (range 146–602 ng ml^{-1}) at the end of the infusion (table III). The concentration–time profile for the two patients with the lowest and highest steady-state concentrations are shown in figure 2. The mean plasma alfentanil concentration–time profile for all patients, and the resulting fit to these data are shown in figure 3. The mean values (±SD) of the rate constants (k_{10}, k_{12} and k_{21}) were 1.20±0.52, 1.83±0.72 and 1.29±0.47 h^{-1}, respectively.

TABLE III. *The individual plasma alfentanil concentrations and the time interval from termination of infusion to the first analgesic dose of ketobemidone given during the first 6 h after operation. * Required naloxone 0.1 mg*

	Plasma alfentanil concentration			
Patient No.	at end of infusion (ng ml^{-1})	at extubation (ng ml^{-1})	at the first analgesic (ng ml^{-1})	Time to the first analgesic (min)
1	146	85	28	125
2	199	130	51	155
3	195	75	—	—
4	359	260*	110	245
5	228	130	21	300
6	334	160	40	275
7	219	140	—	—
8	364	290*	190	110
9	602	370*	—	—
10	266	195	—	—

The total plasma clearance of alfentanil ranged between 93 and 431 ml min^{-1} (mean 249 ml min^{-1}). When adjusted to body weight, the plasma clearance ranged between 1.22 and 7.42 ml min^{-1} kg^{-1}.

The apparent volume of distribution varied four-fold, from 0.25 to 0.96 litre kg^{-1}, with a mean of 0.58 litre kg^{-1}. The variation in the apparent volume of distribution at steady-state was less, with a range from 0.27 to 0.64 litre kg^{-1} (mean 0.44 litre kg^{-1}). The terminal elimination half-life of alfentanil ranged between 72 and 170 min (mean 112 min).The individual pharmacokinetic parameters are presented in table IV.

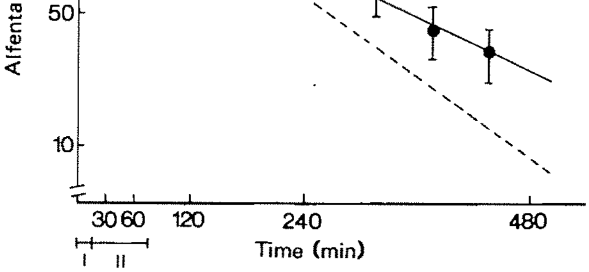

FIG. 3. Mean (±SEM) alfentanil concentration–time profile. The solid line shows the fit and the broken line the simulated concentrations. I and II represent the durations of the first and second infusions, respectively.

Three of the patients required naloxone because of respiratory depression at the time of extubation. In these patients the plasma concentration of alfentanil averaged 307 ng ml^{-1}. The corresponding mean plasma concentration in those who did not require naloxone ($n = 7$) was 131±41 ng ml^{-1} (table III). This difference is statistically significant (Wilcoxon rank sum test: $P < 0.02$).

Six patients required supplementary analgesia during the first 6 h after termination of the infusion; of these, two had been given naloxone. The mean time from the end of the infusion to the first dose of analgesic was 201 min, and at the time of this dose the mean plasma concentration of alfentanil was 73 ng ml^{-1} (range 21–190 ng ml^{-1}). The concentrations in the two patients who were also given naloxone were 110 and 190 ng ml^{-1}, which may be compared with the mean value of 35 ng ml^{-1} (range 21–51 ng ml^{-1}) in the other four patients (table III).

DISCUSSION

It is desirable that drugs used in a total i.v. technique have a prompt and stable effect during surgery and that this effect ceases rapidly once the infusion is terminated. I.v. agents used in anaesthesia usually have residual postoperative side effects such as respiratory depression, excessive sedation and somnolence, resulting in prolonged recovery. The dynamics and kinetics of alfentanil,

TABLE IV. *Individual pharmacokinetic variables of alfentanil in 10 surgical patients: total plasma clearance* (Cl), *volume of the central compartment* (V_1) *apparent volume at steady-state* (Vd^{ss}), *apparent volume of distribution* (Vd^{β}) *and the elimination half-life* ($T_{\frac{1}{2}}^{\beta}$)

Patient No.	*Cl* (ml min^{-1})	V_1 (ml kg^{-1})	Vd^{ss} (litre kg^{-1})	Vd^{β} (litre kg^{-1})	$T_{\frac{1}{2}}^{\beta}$ (min)
1	393	182	0.53	0.76	72
2	285	167	0.54	0.85	137
3	431	188	0.64	0.96	125
4	198	195	0.36	0.25	78
5	282	257	0.49	0.72	113
6	199	182	0.37	0.50	115
7	282	256	0.51	0.85	104
8	144	151	0.29	0.32	103
9	93	101	0.27	0.30	170
10	183	221	0.44	0.49	104
Mean	249	190	0.44	0.58	112
±SD	106	47	0.12	0.25	28
CV (%)	43	25	27	43	25

with its rapid onset of action resulting from fast distribution to the brain [10], together with its rapid plasma elimination [5], make it a promising analgesic for total i.v. anaesthesia. The lack of pharmacologically active metabolites [11] and the absence of significant interactions with other drugs are other advantages which further emphasize the suitability of alfentanil.

Pharmacokinetics

The total body clearance of a drug determines the plasma concentration at steady-state. The mean total plasma clearance of alfentanil in the present study (249 ml min^{-1}) was of the same order as that previously observed in healthy volunteers [12]. Thus the influence of the surgical procedure, and of other concomitantly administered drugs, on the clearance of alfentanil seems to be negligible. Alfentanil is eliminated mainly by hepatic metabolism and the hepatic extraction ratio can be calculated to be about 0.3, assuming a blood:plasma ratio of 0.63 [13]. The clearance of such a drug is dependent upon protein binding in the plasma and intrinsic hepatic clearance [14]. Thus, possible changes in hepatic blood flow during the surgical procedure are probably of only minor interest, since the clearance value indicates flow-independent hepatic elimination. On the other hand, a possible increase in the plasma concentration of α_1-acid glycoprotein during the surgical procedure may decrease the clearance.

The most useful volume term for describing the apparent distribution space in a multicompartment system is the volume of distribution at steady-state (Vd^{ss}). The apparent volume of distribution (Vd^{β}) of alfentanil is dependent on the drug elimination and overestimates Vd^{ss}, since this drug is rapidly cleared from the central compartment. Vd^{ss} is independent of drug elimination. The restricted distribution of alfentanil contrasts with that of other opioids such as fentanyl, morphine and pethidine. This difference may be explained by factors such as the high plasma protein binding and the low lipid solubility of alfentanil.

The time taken for the concentration of a drug to reach steady-state is dependent upon the elimination half-life. A short half-life, as a result of a small volume of distribution rather than of high clearance, may facilitate the attainment of a steady-state value in plasma during a relatively short infusion period. The mean ratio of β/k_{10} for alfentanil is 0.31, as compared with 0.14 and 0.07 for fentanyl and morphine, respectively [12, 15]. The ratio indicates how "two compartment" a drug is. A small value denotes a drug with a greater fraction in the peripheral compartment. Thus, the rapid distribution of alfentanil because of its small volume of distribution suggests that it is a drug for which steady-state is more rapidly attained than in the case of other opioids.

The infusion regimen

It was the aim in the present study to reach a steady-state plasma concentration of 300 ng ml^{-1}. The mean observed plasma concentration at the end of the infusion (291 ng ml^{-1}) was very close to the predicted concentration. The plasma clearance, however, varied more than four-fold, resulting in large interindividual differences in concentration at the end of the infusion (fig. 2, table III). These differences in plasma clearance were probably caused by variation in the hepatic metabolic capacity [16]. Furthermore, interindividual differences in protein binding may also influence clearance. Even so, the attempt to achieve steady-state can be considered successful, since the concentration was stable in most patients during the maintenance infusion.

The accuracy of using average pharmacokinetic data to design infusion regimens could be evaluated by comparing the predicted with the observed concentrations. The correlation between the predicted and mean observed plasma concentrations was excellent during the maintenance infusion (fig. 3). However, the large variation in observed concentrations at steady-state (fig. 2) demonstrate the difficulty in predicting doses for individual patients. There was a difference between predicted and mean observed concentrations after the infusion, since the terminal half-life found in the present study was somewhat longer than the value used for the simulation (tables II, IV).

Fragen and colleagues [5] used the combination of a bolus (80 μg kg^{-1}) with a single constant i.v. infusion (3 μg kg^{-1} min^{-1}) to achieve rapidly and maintain plasma concentrations necessary to provide adequate analgesia. The advantage of the present infusion regimen over that used by Fragen and colleagues is that prolonged infusion will not result in increasing concentrations of alfentanil (fig. 1). A high concentration at the end of an infusion will lead to postoperative respiratory depression. The disadvantage of a fixed infusion rate is that no consideration is paid to the interindividual variation in the pharmacokinetics or to the varying degree of surgical stimulation. Our maintenance infusion rate of 1.0 μg min^{-1} kg^{-1} is in accord with published data on the dose requirements of alfentanil in combination with nitrous oxide [17].

The postoperative period

There seems to be a correlation between respiratory depression and plasma alfentanil concentration, and the three patients with significantly higher concentrations than the others at the time of extubation were given naloxone to restore adequate ventilation (table III).

The mean plasma concentration at the time when supplementary analgesia was required (73 ng ml^{-1}) ($n = 6$) is an indication of the minimum analgesic plasma concentration of alfentanil reached in the postoperative period. This minimum plasma concentration, however, showed a large interindividual variation, which could be explained by the concomitant administration of midazolam or by variations in the endogenous pain inhibitory system—that is, the endorphine system, a determinant of postoperative analgesic requirement [18]. Furthermore, the administration of naloxone at the time of extubation in two of these patients may have influenced the value. The mean plasma concentration of 35 ng ml^{-1} found for the four patients who did not require naloxone, may be a better indication of the minimum effective analgesic concentration of alfentanil.

CONCLUSION

Alfentanil has a rapid distribution and a short half-life which are not influenced by anaesthesia or concomitantly administered midazolam. Furthermore, the pharmacokinetic properties of alfentanil in combination with its high analgesic potency make it suitable for infusion in a total i.v. technique. Consideration must be paid, however, to interindividual variations in the pharmacokinetic data, and to variations in analgesic requirements during the various stages of surgery.

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PHARMACOKINETICS OF MIDAZOLAM IN ANAESTHETIZED CIRRHOTIC PATIENTS

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SUMMARY

The pharmacokinetics of midazolam were compared in cirrhotic patients ($n = 10$) and control patients ($n = 9$), during general anaesthesia. Total plasma clearance was 637 ± 223 ml min^{-1} (mean ± SD) in control patients and 402 ± 170 ml min^{-1} in cirrhotic patients ($P < 0.05$). The total volume of distribution was similar. Elimination half-life was 135 ± 40 min in controls and 168 ± 30 min in cirrhosis ($P < 0.05$). Protein binding was evaluated by equilibrium dialysis in both groups at two concentrations of midazolam: 20 and 500 µg litre^{-1}. No saturation occurred, but the free fraction was 4.9 ± 1.7% in cirrhotic patients, compared with 1.9 ± 0.6% in controls ($P < 0.01$). Despite its mainly hepatic elimination, midazolam disposition appears to be only slightly impaired in cirrhotic patients.

Midazolam maleate, a water soluble benzodiazepine derivative, is used widely in anaesthetic practice as a premedicant and for induction of anaesthesia. Compared with other benzodiazepines, midazolam has a relatively rapid onset of action and high metabolic clearance with an elimination half-life ranging from 1.5 to 3 h [1–3]. Midazolam is eliminated almost exclusively by hepatic biotransformation, mainly via hydroxylation followed by conjugation [1, 2, 4]. Less than 0.02% of an administered dose is excreted unchanged in the urine [3] and the hepatic extraction ratio is estimated to be 0.3–0.5 [4, 5].

Since midazolam is eliminated by hepatic metabolism, one would expect liver disease to impair metabolism and hence plasma clearance. In healthy subjects, the protein bound fraction of midazolam is estimated to be 96–98% [6]. An increase in free fraction of midazolam has been observed in patients with chronic renal failure associated with an increase in both plasma clearance and total apparent volume of distribution, with no change in terminal half-life [7]. An increased free fraction has been observed for other anaesthetic agents also, in patients with cirrhosis [8–10].

It is therefore of interest to determine if cirrhosis, which is known to impair both hepatic function and protein binding [11], modifies midazolam dispostion during anaesthesia. This study was designed to compare the pharmacokinetic parameters of midazolam in anaesthetized cirrhotic and healthy patients.

PATIENTS AND METHODS

Patients

After obtaining approval from the institutional human studies committee and informed consent, we studied nine patients, ranging in age from 22 to 52 yr (mean ± SD = 30 ± 3.5 yr) and with normal hepatic and renal function, undergoing elective surgery, and 10 patients ranging in age from 42 to 75 yr (59 ± 12 yr), with cirrhosis (table I). Alcoholism was the cause of liver disease in all the patients and cirrhosis was confirmed by histological examination of a liver biopsy. None of the

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TABLE I. *Characteristics and liver function tests of cirrhotic patients. —Data not available*

Patient No.	Sex	Age (yr)	Surgical procedure	SGPT (iu ml^{-1})	Serum alkaline phosphatase (iu ml^{-1})	Serum bilirubin (μmol litre^{-1})	Prothrombin (% of control)
1	M	41	Portocaval shunt	24	113	35	66
2	M	44	Splenorenal shunt	68	106	29	78
3	M	61	Splenorenal shunt	34	109	24	59
4	M	75	Sclerosis of oesophageal veins	23	71	25	59
5	F	57	Sclerosis of oesophageal veins	17	123	—	70
6	M	60	Sclerosis of oesophageal veins	23	67	13	70
7	M	74	Sclerosis of oesophageal veins	25	62	—	24
8	F	73	Sclerosis of oesophageal veins	18	75	51	68
9	M	57	Sclerosis of oesophageal veins	12	59	16	62
10	M	45	Sclerosis of oesophageal veins	22	162	31	100
Normal value				<20	<30	<17	

patients with cirrhosis had ascites at the time of the study or haemorrhage within 2 weeks before operation. No patient was receiving chronically, medication known to be enzyme inducing or inhibiting, and none had ingested alcohol for at least 1 week before the study. Control patients ($n = 9$) underwent elective abdominal surgery which consisted of cholecystectomy (four), hysterectomy (three) or repair of inguinal hernia (two). Cirrhotic patients ($n = 10$) underwent either sclerosis of oesophageal varices (seven) or portocaval shunt (three) (table I). Only one patient undergoing portocaval shunt required transfusion of blood during the operation (2 units).

Premedication consisted of lorazepam 2.5 mg by mouth 2 h before anaesthesia, which was induced with midazolam 0.2 mg kg^{-1} i.v. given over 15 sec. An additional dose of thiopentone 2 mg kg^{-1} was administered i.v. Vecuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was maintained with 60% nitrous oxide in oxygen and the lungs were ventilated artificially to maintain the end-tidal carbon dioxide concentration at approximately 5% (Datex CO_2 analyser). Vecuronium was administered in repeated doses of 0.025 mg kg^{-1} to provide adequate muscle paralysis. Repeated doses of fentanyl 1.5 μg kg^{-1} were administered when analgesia was required.

Multiple blood samples were drawn into glass tubes containing EDTA at 0, 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 h after drug administration; plasma was separated after centrifugation and frozen at −20 °C until required for analysis.

Analytical methods

The plasma samples were assayed for unchanged midazolam by electron capture gas–liquid chromatography, according to the method of Greenblatt and colleagues [12]. The intra- and inter-assay coefficients of variation were 4 and 9%, respectively, at a concentration of 500 μg litre^{-1}, and 10 and 15%, respectively, at a concentration of 10 μg litre^{-1}. The sensitivity was 5 μg litre^{-1}. Metabolites were not determined, but these did not interfere with the assay of midazolam, nor did lorazepam, its metabolites or thiopentone.

The extent of midazolam binding to plasma proteins was determined by equilibrium dialysis using purified ^{14}C-midazolam (Hoffmann-La Roche, Basel, Switzerland) at concentrations of 20 and 500 μg litre $^{-1}$ and using plasma collected before operation from each patient in both groups. The radiopurity of ^{14}C-midazolam, checked by thin layer chromatography, was 98%. An equilibrium dialyser composed of 2-ml Teflon cells and dialysis membranes (molecular weight cutoff

= 2000) was used. Plasma samples of 1 ml, containing the desired concentration of midazolam, were dialysed against 1 ml of phosphate buffer 0.067 mol litre^{-1} at pH 7.4. A preliminary study showed that dialysis equilibrium was reached within 90 min, therefore a dialysis of 2 h was chosen with a rotation speed of 20 rev min^{-1} in a drive system maintained at 37 °C. After dialysis, the drug concentration in the buffer, which was taken as free-drug fraction, and the drug in the plasma, which was taken as the sum of bound and free fractions, were measured by liquid scintillation counting. The percent of unbound fraction was calculated as the free drug concentration in the buffer divided by the total post-dialysis concentration in the plasma.

Data analysis

Total midazolam concentrations *v.* time were used to calculate the pharmacokinetic parameters for each patient, using a model-independent approach. The area under the curve from 0 to infinity (AUC_{extra}) was calculated using the conventional trapezoidal rule and extrapolation method, with the rate constant for elimination (β) determined from linear regression of the post-distributional natural log of plasma concentrations *v.* time slope. The total plasma clearance was determined by dividing the dose by the AUC_{extra}. The steady state volume of distribution (Vd^{ss}) was evaluated by the non-compartmental method described by Benet and Galeazzi [13]. The total apparent volume of distribution (Vd^{AUC}) was measured as follows:

$$Vd^{AUC} = \frac{\text{dose}}{\beta \times AUC}$$

A two-tailed Mann–Whitney U test ($P < 0.05$) was used for statistical comparisons between the values obtained in control and cirrhotic patients. Paired Student's t tests were used to compare the degree of protein binding of midazolam at the two concentrations studied.

RESULTS

The midazolam plasma concentration decay curves were biexponential for both groups (fig. 1). AUC_{extra} was increased by 57 % in the cirrhotic patients compared with the control group ($P < 0.05$). $T_{\frac{1}{2}}^{\beta}$ was longer by 25 % (135 ± 40 min in the control group, compared with 168 ± 30 min in cirrhotic patients) (table II).

Total plasma clearance was 637 ± 223 ml min^{-1} in the control group and was significantly lower, by 37 % ($P < 0.05$), in cirrhotic patients. Vd^{AUC} and Vd^{ss} were not significantly modified (table II).

In cirrhotic patients, the midazolam free fraction was 4.9 ± 1.7 %, and was significantly greater ($P < 0.01$) than the value of 1.9 ± 0.6 % in control patients (table III). For the two concentrations studied in each patient, no significant difference in binding values was observed between the lowest

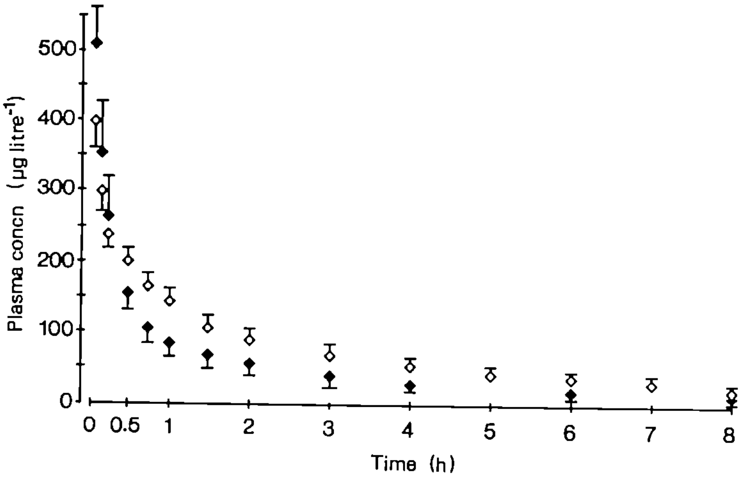

FIG. 1. Time course of plasma concentration of midazolam in control (◆) and cirrhotic (◇) patients, after a single i.v. dose (2 mg kg^{-1}). Each point represents mean ± SEM of 10 or nine determinations, in cirrhotic and control patients, respectively.

TABLE II. *Midazolam pharmacokinetics in control patients and those with cirrhosis.* *$P < 0.05$ v. *controls*

Subjects	AUC_{extra} (mg ml^{-1} h^{-1})	$T_{\frac{1}{2}}^{\beta}$ (min)	Cl (ml min^{-1})	Vd^{ss} (litre)	Vd^{AUC} (litre)
Control					
1	371	126	540	53	75
2	236	108	903	120	134
3	655	192	396	82	110
4	630	204	390	106	108
5	482	126	552	94	103
6	197	84	1040	102	123
7	450	114	532	85	87
8	313	150	765	150	166
9	392	114	612	100	102
Mean	414	135	637	99	111
SD	159	40	223	27	27
Cirrhosis					
1	403	162	580	136	137
2	359	120	743	117	127
3	737	192	340	80	94
4	522	162	542	95	131
5	544	204	307	75	90
6	561	150	357	63	77
7	695	156	382	84	86
8	588	132	340	64	66
9	1193	204	182	45	45
10	892	192	243	63	67
Mean	649	168*	402*	82	92
SD	247	30	170	27	31

TABLE III. *Plasma albumin concentration and midazolam free fraction (mean ± SD).* **$P < 0.01$ v. *controls*

	Albumin (g litre^{-1})	Free fraction (%) at midazolam concentration of	
		20 µg litre^{-1}	500 µg litre^{-1}
Control	39 ± 6	1.9 ± 0.6	1.7 ± 0.6
Cirrhosis	35 ± 5	4.9 ± 1.7**	4.8 ± 2.0**

and highest concentrations (table III). However, at both concentrations, the free fraction was significantly higher in the cirrhotic population than in the controls. The mean plasma concentration of albumin was 34 ± 5 g litre^{-1} in patients with cirrhosis; this did not differ significantly from the value of 39 ± 6 g litre^{-1} observed in control patients.

DISCUSSION

We have observed a smaller total clearance and a larger free fraction of midazolam in cirrhotic compared with healthy patients. The total clearance was smaller by approximately 37% in the former group, and there was no significant difference in the total volume of distribution, leading to a slight, but significantly greater, elimination half-life in cirrhotic patients.

No clinical difference in onset of action of midazolam was observed in the cirrhotic patients compared with control subjects. The duration of action of midazolam could not be estimated since other anaesthetic agents were administered simultaneously.

Midazolam is eliminated almost exclusively by the liver and its hepatic extraction ratio has been estimated at 0.3–0.5 in normal subjects by comparing its plasma clearance with hepatic blood flow. However, this estimate is questionable since the hepatic blood flow may vary considerably during anaesthesia. The main determinants of midazolam elimination are the capacity of the drug metabolizing system (intrinsic clearance) and the hepatic blood flow [14]. These two factors may be reduced in patients with cirrhosis [15] and may contribute to the reduced clearance of midazolam. The effective blood flow may be reduced in cirrhosis as a result of a reduction in total blood flow or of the development of intrahepatic vascular shunts [16].

The modifications observed in this study of midazolam disposition in cirrhosis are small compared with studies of other benzodiazepines. The plasma clearance of diazepam was observed to be 50 % smaller in cirrhotic patients, causing a significant increase in elimination half-life (106 h *v.* 47 h) in age-matched control subjects [17]. The minor alterations in midazolam pharmacokinetics observed here may be explained by the moderate degree of liver dysfunction in the patients with liver disease, none having decompensated liver cirrhosis. In comparison, Rinetti and colleagues [18] observed no change in midazolam disposition following oral administration of the drug to patients with compensated liver cirrhosis, whereas Macgilchrist and colleagues [19] observed a two-fold prolongation of the elimination half-life of midazolam as a result of decreased clearance in cirrhotic patients with end-stage liver failure.

The variation in plasma binding may be an additional factor which modified clearance. In control patients, midazolam is bound extensively to plasma proteins (but without saturation in the concentration range studied (20–500 μg litre^{-1})). As with other anaesthetic agents [8–10] in the cirrhotic population, a smaller degree of midazolam protein binding was observed. Albumin appears to be the major source of binding of midazolam [20]. However, there was no significant difference in albumin concentrations in the two groups. Thus it is possible that qualitative differences in the binding proteins, accumulation of endogenous binding inhibitors such as bilirubin [11], or both, may explain the smaller degree of midazolam protein binding in cirrhotic individuals. Consequently, an increased free fraction may enhance the pharmacological effect of midazolam in patients with cirrhosis.

Patients with cirrhosis were older than the controls; age is known to alter the pharmacokinetics of midazolam [21]. In elderly volunteers, Greenblatt and colleagues [21] observed an increase in elimination half-life and a decrease in plasma clearance of midazolam in males only. In surgical patients Harper and colleagues [22] observed a significant increase in the elimination half-life of those undergoing minor surgery, but no change in plasma clearance. It is possible, therefore, that the smaller plasma clearance observed in the cirrhotic patients in the present study is partly a result of the older age. However, only three patients with cirrhosis exceeded 70 yr and therefore ageing alone is unlikely to account for the 36 % smaller plasma clearance in the cirrhotic patients.

In conclusion, after a single i.v. bolus, midazolam disposition in cirrhotic subjects appears to be only slightly impaired, despite its hepatic dependent elimination. The changes are probably of little clinical importance when a single dose is given. However, when midazolam is administered to cirrhotic patients by multiple dosing or i.v. infusion, delayed elimination and increased pharmacological effects should be expected.

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PULMONARY BLOOD FLOW DURING CLOSED HEART SURGERY

Use of a Modified $\dot{Q}p/\dot{Q}s$ Ratio to Assess Adequacy of Palliation of Systemic–Pulmonary Artery Shunts

A. P. B. YATES

SUMMARY

The ability to assess changes in pulmonary blood flow, using a modified $\dot{Q}p/\dot{Q}s$ ratio ($\dot{Q}p/\dot{Q}s_{mod}$), was evaluated in 12 infants with congenital heart disease and complete intracardiac mixing who underwent modified Blalock–Taussig shunt procedures. At the various measuring stages there were no major changes in mean arterial pressure or heart rate. Arterial oxygen tensions and saturation increased ($P < 0.01$) and the arterial to end-tidal carbon dioxide difference ($Pa_{CO_2} - PE'_{CO_2}$) was significantly reduced ($P < 0.001$) after completion of the shunt procedure. There was a significant increase in mean $\dot{Q}p/\dot{Q}s_{mod}$ after chest closure ($P < 0.001$), which was seen to correlate well with early clinical outcome. Two patients who did not demonstrate any increase in $\dot{Q}p/\dot{Q}s_{mod}$ over the course of the procedure had failed shunts. The limitations of use of the $\dot{Q}p/\dot{Q}s_{mod}$ are discussed. A modified $\dot{Q}p/\dot{Q}s$ ratio of less than unity after surgery is strongly indicative of inadequate palliation.

Infants with complex congenital heart disease that is not amenable to early correction, and who present with critically reduced pulmonary blood flow, often require palliative surgery to improve their haemodynamic status and to allow continued growth [1]. The creation of systemic–pulmonary artery shunts of the type described by Blalock and Taussig [2] is an attempt to improve pulmonary perfusion without causing excessive flow. The present study evaluated the ability to assess changes in pulmonary blood flow, using a modified pulmonary to systemic flow ratio, in infants with congenital heart disease who undergo modified Blalock–Taussig shunt procedures.

The techniques and limitations of using the Fick principle to express the ratio of pulmonary blood flow to systemic blood flow ($\dot{Q}p/\dot{Q}s$) during cardiac catheterization have been reviewed previously [3–5]. If intracardiac mixing is complete, it is necessary to modify the formula:

$$\frac{\dot{Q}p}{\dot{Q}s} = \frac{Sao_{O_2}(\%) - S\bar{v}_{O_2}(\%)}{S\textsc{pv}_{O_2}(\%) - S\textsc{pa}_{O_2}(\%)}$$

where ao = aorta, v̄ = mixed venous, PV = pulmonary vein and PA = pulmonary artery. Under these circumstances $S\textsc{pa}_{O_2}$ is identical to Sao_{O_2} and, accordingly:

$$\frac{\dot{Q}p}{\dot{Q}s} = \frac{Sao_{O_2}(\%) - Ssvc_{O_2}(\%)}{S\textsc{pv}_{O_2}(\%) - Sao_{O_2}(\%)}$$

where SVC = superior vena cava.

With complete intracardiac mixing and in the presence of atrial shunting, superior vena caval saturation may be the best representation of mixed venous oxygen saturation. If blood returning in the pulmonary veins is considered fully saturated (this assumes there are no significant respiratory causes for hypoxaemia), the $\dot{Q}p/\dot{Q}s$ ratio may be further approximated to:

$$\frac{\dot{Q}p}{\dot{Q}s_{mod}} = \frac{Sa_{O_2}(\%) - Ssvc_{O_2}(\%)}{100 - Sa_{O_2}(\%)}$$

where a = arterial.

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PATIENTS AND METHODS

Only infants with anatomical abnormalities compatible with complete intracardiac mixing were included in the study. These abnormalities included the presence of a single atrio–ventricular connection (tricuspid atresia), a univentricular heart or a single ventricular–arterial outlet (pulmonary atresia). The diagnosis was confirmed by physical examination, two-dimensional echocardiography and findings during cardiac catheterization. The selected group consisted of 12 patients (age 2 days to 11 months) with body weights ranging from 2.6 to 8.1 kg. Further patient data are given in table I. The study was approved by the Hospital Ethics Committee.

Food was withheld from the patients for at least 4 h before surgery. Infants weighing less than 8 kg were premedicated only with atropine 0.15–0.2 mg i.m. One infant who weighed 8.1 kg received, in addition, pethidine compound 0.6 ml i.m. (1 ml contains: pethidine 25 mg, chlorpromazine 6.25 mg, promethazine 6.25 mg). All neonates younger than 7 days old received prostaglandin E_1 by infusion (0.01–0.02 $\mu g\ kg^{-1}\ min^{-1}$) to maintain ductal blood flow.

Awake intubation was performed where appropriate, otherwise anaesthesia was induced with cyclopropane in oxygen ($F_{I_{O_2}} = 0.5$) and tracheal intubation performed after administration of suxamethonium 1–1.5 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen ($F_{I_{O_2}} = 0.5$) and fentanyl 0.003–0.005 mg kg^{-1}. Radial artery and internal jugular vein cannulae were inserted and the lungs were mechanically ventilated with an Engström 2000 ventilator. Muscle paralysis was achieved with pancuronium 0.1–0.2 mg kg^{-1}. An in-line capnometer (Hewlett–Packard 14360A), which had been calibrated with carbon dioxide of known concentration within the measuring range, was placed at the tracheal tube connector. The signal was corrected for the presence of nitrous oxide and for the oxygen concentration.

Arterial and central venous pressures were measured with Hewlett–Packard 1290 pressure transducers and, together with the ECG, recorded continuously on a Hewlett–Packard 775 B monitoring system. Pulse oxygen saturation (Ohmeda Biox 3700) was recorded from the hand opposite to the side of the shunt and displayed continuously. Samples (0.5 ml) of arterial and central venous blood (in heparinized syringes) were analysed within 5 min of sampling in a conventional blood-gas analyser (Corning 168) and a co-oximeter (Radiometer OSM 2), both of which were calibrated daily. In all patients body temperature ranged between 36 and 37 °C during measurements.

Procedure

After the induction of anaesthesia, tracheal intubation and the placement of appropriate arterial and venous cannulae, mechanical ventilation was continued at an unchanged setting for at least 15 min before the first set of measurements was obtained—before the start of surgery. The next measurements were performed after thoracotomy with the lung retractors in place. All patients underwent the creation of a modified Blalock–Taussig shunt (MBTS), as described by

TABLE I. *Patient characteristics. PA = pulmonary atresia; PS = pulmonary stenosis; TS = tricuspid stenosis; ASD = atrial septal defect; VSD = ventricular septal defect; DOV = double outlet ventricle; PDA = persistent ductus arteriosus*

Patient No.	Age (month/day)	Body wt (kg)	Hb ($g\ dl^{-1}$)	Hct (%)	Diagnosis
1	9/0	8.1	14.3	43.1	PA; ASD; VSD; DOV
2	0/4	3.3	17.0	54.0	PA; PDA; DOV
3	0/7	2.6	15.2	52.0	PA; PDA; ASD
4	0/3	2.6	17.0	53.0	PA; TS; VSD; PDA
5	0/2	2.7	15.0	50.0	PA; ASD; VSD; DOV; PDA
6	11/26	7.9	12.2	39.0	TA; PS; ASD; VSD
7	0/10	3.3	14.2	45.0	PA; PDA; DOV
8	0/2	3.0	14.8	45.4	TA; PS; ASD; PDA
9	0/2	3.1	14.9	46.3	PA; PDA
10	0/11	4.0	15.9	49.0	PA; ASD; DOV
11	0/2	2.8	14.8	41.9	PA; VSD; PDA
12	0/3	3.2	18.6	59.1	PA; VSD; PDA

TABLE II. *Mean values (SEM) of mean arterial pressure (MAP), heart rate (HR), arterial blood-gas tensions, arterial oxygen saturation* (Sa_{O_2})*, superior vena caval oxygen saturation* ($Ssvc_{O_2}$)*, end-tidal carbon dioxide tension* (PE'_{CO_2}) *and modified pulmonary to systemic blood flow ratio* ($\dot{Q}p/\dot{Q}s_{mod}$) *at different stages of measurement. Statistically significant differences:* *$P < 0.01$, **$P < 0.001$ *between measurements before surgery and after chest closed*

	Before surgery	After thoracotomy	Just after anastomosis	Chest closed
MAP (mm Hg)	56 (4)	52 (4)	55 (3)	56 (3)
HR (beat min^{-1})	152 (4)	157 (4)	160 (5)	159 (6)
pH	7.42 (0.02)	7.41 (0.02)	7.40 (0.01)	7.42 (0.02)
Pa_{CO_2} (kPa)	3.62 (0.20)	3.96 (0.30)	3.74 (0.21)	3.79 (0.24)
Pa_{O_2} (kPa)	5.60 (0.31)	5.15 (0.43)	6.40 (0.41)	7.37 (0.60)*
Sa_{O_2} (%)	74 (4)	68 (5)	80 (3)	87 (2)*
$Ssvc_{O_2}$ (%)	61 (5)	53 (6)	56 (5)	61 (6)
PE'_{CO_2} (kPa)	2.32 (0.16)	2.41 (0.23)	2.98 (0.22)	3.19 (0.22)*
$\dot{Q}p/\dot{Q}s_{mod}$	0.6 (0.1)	0.5 (0.1)	1.4 (0.2)	2.0 (0.2)**

de Leval and associates [6], using a 5-mm prosthetic graft. Immediately after completion of the anastomosis and the removal of the clamps, further measurements were undertaken. The final set of measurements was carried out when the thoracotomy had been closed with the patient still on the operating table. Three patients required dopamine 2.5–5.0 µg kg^{-1} min^{-1} to maintain shunt perfusion pressure.

Statistics

Mean values, standard deviations (SD) and standard errors of the mean (SEM) were calculated. The results were evaluated by paired *t* tests, and $P < 0.05$ was considered statistically significant.

RESULTS

At the various measuring stages there were no major changes in mean arterial pressure (MAP) or heart rate (table II). Arterial oxygen tensions and saturation increased after the formation of the MBTS and were improved ($P < 0.01$) after closure when compared with values obtained before surgery. There was no significant difference in pH, arterial carbon dioxide tension (Pa_{CO_2}) or $Ssvc_{O_2}$ over the course of surgery (table II).

Before surgery, the difference between the mean (SEM) Pa_{CO_2} of 3.62 (0.20) kPa and the end-tidal carbon dioxide concentration (PE'_{CO_2}) of 2.32 (0.16) kPa was 36% ($P < 0.01$), with this difference also noted after thoracotomy ($P < 0.01$). After completion of the MBTS and closure of the chest the arterial to end-tidal carbon dioxide difference ($Pa_{CO_2} - PE'_{CO_2}$) was significantly reduced ($P < 0.001$).

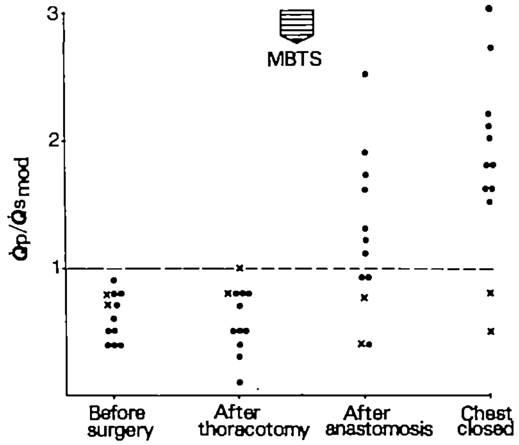

FIG. 1. Values of $\dot{Q}p/\dot{Q}s_{mod}$ for all patients at the four measuring stages. Individual values for the two patients (Nos 2 and 6) whose shunts failed are differentiated (x). MBTS = Modified Blalock–Taussig shunt.

Table II shows the changes the mean Qp/Qs_{mod} at the four measuring stages, individual results are shown in figure 1. There was a significant increase in mean $\dot{Q}p/\dot{Q}s_{mod}$ after chest closure when compared with values before surgery ($P < 0.001$).

There were no hospital deaths within the study group. Adequacy of palliation—as indicated by early postoperative recovery —was satisfactory in all but two patients. These two (Nos 2 and 6) did not demonstrate any increase in $\dot{Q}p/\dot{Q}s_{mod}$ over the course of the procedure (fig. 1). Both patients had no detectable shunt murmur after surgery, with radiological evidence of continuing pulmonary oligaemia. Weaning from mechanical ventilation proved impossible and shunt occlusion was confirmed angiographically. Both underwent further surgery (shunt revision in one case, creation of contralateral MBTS in the other) before they could be successfully weaned from mechanical ventilation.

DISCUSSION

It has been claimed that modified Blalock–Taussig shunt offers the best palliation in patients with pulmonary hypoperfusion because the diameter of the subclavian artery is especially suitable to control pulmonary blood flow [1]. Intraoperative complications include kinking and distortion of the pulmonary artery and occlusion of the shunt [6], all of which affect haemodynamic stability. The ability to assess changes in pulmonary blood flow objectively during operation would provide a useful early indicator of the adequacy of palliation.

It has been suggested that the $P\text{E}'_{CO_2}$ may be used as an indicator of pulmonary blood flow during closed heart surgery in infants [7]. This, however, assumes that the level of ventilation is held constant—an assumption which may be invalid, especially if mechanical ventilation by hand is used in the presence of surgical retraction. In this study, although there was no statistical difference between mean arterial carbon dioxide tensions at the four measuring stages (table II), considerable scatter was found in individual patients. The $(Pa_{CO_2} - P\text{E}'_{CO_2})$ difference has been related to abnormal lung perfusion by Heneghan, Scallan and Branthwaite [8], based on peroperative measurements during pulmonary artery surgery. If in this study, the $(Pa_{CO_2} - P\text{E}'_{CO_2})$ difference is used and plotted against the modified $\dot{Q}p/\dot{Q}s$ at all measuring stages, a curvilinear relationship is obtained (fig. 2). Although there is a widening $(Pa_{CO_2} - P\text{E}'_{CO_2})$ difference when the $\dot{Q}p/\dot{Q}s_{mod}$ is less than unity, this relationship no longer applies as pulmonary blood flow is increased.

Non-invasive pulse oximetry is being used increasingly to detect changes in oxygen saturation during surgical manipulations that alter pulmonary artery blood flow [9]. The advantage is that with individual patients desaturation can be detected more quickly than with intermittent blood-gas analysis, and before clinical deterioration of the patient occurs. Whereas continuous pulse oximetry provides an invaluable monitor of systemic oxygenation during the perioperative period, the use of changes in absolute values of arterial and mixed venous oxygen saturation and tension to assess pulmonary blood flow is limited. This is because of their dependence, to a great extent, on factors other than pulmonary blood flow [10, 11].

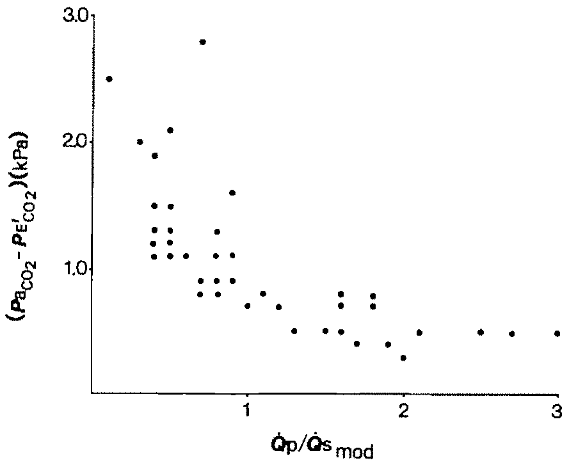

FIG. 2. Values of the arterial to end-tidal carbon dioxide tension differences $(Pa_{CO_2} - P\text{E}'_{CO_2})$ plotted against $\dot{Q}p/\dot{Q}s_{mod}$ for all patients.

The use of the Fick principle [12] to derive the ratio of pulmonary to systemic blood flow involves major assumptions. The results obtained from this and the modified $\dot{Q}p/\dot{Q}s$ can only be approximate, and absolute reliance on numerical accuracy is inappropriate. The use of the modified $\dot{Q}p/\dot{Q}s$ is only applicable in patients with complete intracardiac mixing. Retrospective analysis has shown that 65% of patients undergoing creation of MBTS in this unit had an anatomical diagnosis compatible with the use of the modified $\dot{Q}p/\dot{Q}s$ ratio. With the above limitations accepted, this study confirms that, with appropriate use, the modified $\dot{Q}p/\dot{Q}s$ ratio correlates well with early clinical outcome.

It is proposed that the modified $\dot{Q}p/\dot{Q}s$ ratio provides a simple objective measurement of changes in pulmonary blood flow that can be useful during surgery in selected patients undergoing the creation of systemic–pulmonary artery shunts. A modified $\dot{Q}p/\dot{Q}s$ ratio of less than unity after closure of the chest wall is strongly indicative of inadequate palliation.

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PROTECTION AGAINST MYOCARDIAL ISCHAEMIA BY PRIOR HAEMODILUTION WITH FLUOROCARBON EMULSIONS

N. S. FAITHFULL, M. FENNEMA AND W. ERDMANN

SUMMARY

The possible prophylactic effects of Fluosol-DA 20% (FDA) haemodilution against myocardial hypoxia were studied in two groups of anaesthetized immature pigs. Precalibrated 200-µm diameter oxygen microelectrodes were inserted to the myocardium of the left ventricle. One group of animals was haemodiluted with FDA and both groups received 100% oxygen (plus halothane). The lower one-third of the left anterior descending coronary artery was occluded; this caused no significant cardiovascular changes. Analysis from the microelectrodes in the most hypoxic areas of the myocardium revealed significant decreases in myocardial oxygen tension (Pm_{O_2}*) in the control group 15 min after occlusion, whereas this was not seen until 45 min after occlusion in the FDA-diluted group. Analysis of other electrodes suggested greater hyperaemic compensatory response in ischaemic border areas in the FDA-treated group.*

Fluorocarbons are largely inert chemicals with a high solubility for respiratory and other gases. They are available in emulsified form as the plasma substitute Fluosol-DA 20% (FDA). This has an oxygen solubility of 0.57 ml dl^{-1}/10 kPa [1,2]—about two-and-a-half times that of plasma. To take advantage of this difference, a high inspired concentration of oxygen is usually administered.

Haemodilution with FDA has been shown to decrease myocardial infarction, particularly in relation to the volume of myocardium at risk [3–5]. In a previous study involving measurements of intramyocardial oxygen tension (Pm_{O_2}) we found that haemodilution with FDA 1 h after myocardial infarction could markedly improve tissue oxygenation [6]. The present study was designed to determine if prior haemodilution with FDA could protect against subsequent myocardial ischaemia.

MATERIALS AND METHODS

The model used in these experiments has been described in detail elsewhere [6]. Briefly: two groups of five juvenile Yorkshire pigs (weight range 23.5–27 kg) were anaesthetized with sodium thiopentone 30 mg kg^{-1} i.p. and ventilated with 1.5% halothane in a 2:1 mixture of nitrous oxide and oxygen using a Minivent ventilator to achieve arterial carbon dioxide tensions between 4.7 and 6.0 kPa. Neuromuscular blockade was achieved using pancuronium bromide 0.5 mg kg^{-1} h^{-1} delivered by a Braun Melsungen Perfuser pump.

The right femoral artery was cannulated and a 7-French gauge flow-directed thermodilution catheter was placed in a pulmonary artery via the right femoral vein. Central venous pressure was measured using a catheter inserted to the left femoral vein. All pressures were measured with Gould Statham P23dc transducers and displayed on a 12-channel Grass 7D polygraph. Cardiac output was measured using the thermodilution technique (3500E KMA cardiac output computer).

Arterial and mixed venous blood samples were analysed on a Radiometer ABL1 acid–base laboratory and a Radiometer OSM2 haemoximeter. Derived cardiovascular variables and indices of

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oxygenation were calculated using a Philips P2000 microcomputer. Since fluorocarbons can interfere with the estimation of oxyhaemoglobin using the Radiometer OSM2 [6], oxyhaemoglobin saturation was calculated using the computer subroutine described by Kelman [7] if Fluosol had been administered.

A mid-line thoracotomy was performed, the pericardium was opened and a ligature was placed loosely around the left anterior descending coronary artery (LAD) at the junction of the middle and distal thirds of its length. Pm_{O_2} was measured using 200-µm diameter steel-protected gold microelectrodes (Clark Electromedical Instruments), inserted through a flexible plastic plate which was sewn on to the epicardium. *In situ*, they protruded approximately 3 mm into the myocardium. A reference electrode was embedded in a muscle of the thoracic wall. The electrodes were polarized and the output was amplified and recorded on a Riki-Dinki Recorder Model KA60. The experiments were conducted in an isolated Faraday cage. Electrodes were calibrated before, and at the end of, the definitive study, and results were discarded from any electrode that had drifted more than 7.5 % per hour.

In one group of animals haemodilution was achieved by removal of blood (20 ml kg^{-1}) and immediate volume replacement with FDA. The other group served as controls. When all surgical preparations were completed, the lungs were ventilated with halothane in oxygen for at least 30 min before the LAD was occluded by tightening the perivascular ligature. The experiments were concluded 3 h after occlusion by ventilating the animal's lungs with 100 % nitrous oxide.

Statistical analysis was performed on an Apple IIe microprocessor using paired or unpaired Student's *t* tests as appropriate. Statistical significance was accepted at $P < 0.05$.

RESULTS

Before occlusion of the LAD, cardiac output was significantly greater and systemic vascular resistance was significantly less in the FDA diluted group. Otherwise, there were no significant differences in cardiovascular status (table I).

There were no significant differences in whole body oxygen consumption ($V\text{o}_2$) or flux ($Q\text{o}_2$) (table II).

There were no significant changes in cardiovascular variables or indices of oxygenation after occlusion of the LAD in either group, even though an obvious, macroscopically visible area of infarction was created.

Decreases in $V\text{o}_2$ in the control group following LAD occlusion were not statistically significant. However, at 1, 2 and 3 h after occlusion, values in the control group were significantly lower than

TABLE I. *Changes in systemic cardiovascular variables (mean ± SEM) following terminal left ventricular coronary artery (LAD) occlusion in pigs in control or Fluosol-DA 20 % diluted animals (FDA). Times are given from occlusion.* n = *Number of observations.* * *Significant difference from control group* (P < *0.05*)

	Before LAD occlusion		1 h		2 h		3 h	
	Control	FDA	Control	FDA	Control	FDA	Control	FDA
Heart rate	112	141	123	142	127	148	129	152
(beat min^{-1})	±7.3	±12.9	±8.5	±15.6	±9.6	±20.5	±8.7	±18.2
n	5	5	5	5	5	5	5	5
Mean arterial	10.9	9.7	11.0	9.4	10.7	9.8	12.1	9.71*
pressure (kPa)	±0.47	±0.72	±0.63	±0.56	±1.10	±0.77	±0.54	±0.53
n	5	5	5	5	5	5	5	5
Cardiac output	2.4	3.3*	2.1	3.3*	2.0	3.1*	2.2	2.9
(litre min^{-1})	±0.32	±0.55	±0.21	±0.36	±0.26	±0.36	±0.25	±0.44
n	5	5	5	5	4	5	4	5
Left ventricular	0.022	0.034	0.022	0.026	0.019	0.027	0.025	0.027
minute work (kJ min^{-1})	±0.0025	±0.0067	±0.0026	±0.0040	±0.0038	±0.0038	±0.0032	±0.0048
n	5	5	5	5	4	5	4	5
Systemic vascular	303	138*	320	165*	294	162	304	182
resistance (kPa litre^{-1} s)	±43.2	±15.9	±48.3	±17.1	±70.1	±15.5	±38.2	±26.2
n	5	5	5	5	4	5	4	5

TABLE II. *Changes in whole body oxygen delivery and consumption (mean ± SEM) following terminal left anterior coronary artery (LAD) occlusion in pigs in control or Fluosol-DA 20 % diluted animals (FDA).* n = *Number of observations.* * *Significant difference from control group* (P < *0.05)*

	Before LAD occlusion		1 h		2 h		3 h	
	Control	FDA	Control	FDA	Control	FDA	Control	FDA
Whole body oxygen delivery (ml min^{-1} kg^{-1})	14.3 ±2.69	20.1 ±1.92	13.4 ±2.57	16.6 ±0.96	14.1 ±2.45	18.1 ±1.05	15.9 ±1.67	17.1 ±2.01
n	4	5	4	5	4	5	4	5
Whole body oxygen consumption (ml min^{-1} kg^{-1})	6.2 ±0.75	8.9 ±0.86	5.5 ±0.88	8.9* ±0.57	6.2 ±0.97	9.3* ±0.46	6.8 ±0.38	8.7* ±0.67
n	4	5	4	5	4	5	4	5

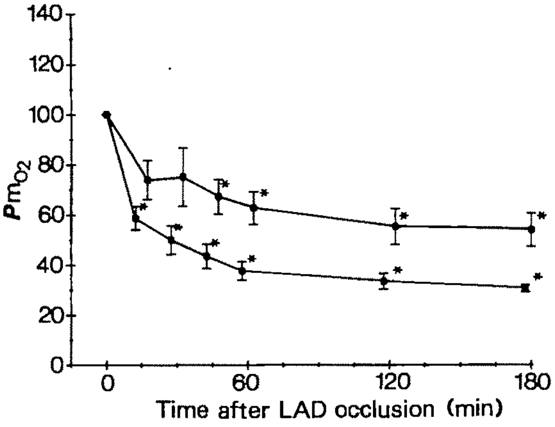

FIG. 1. Percentage changes in myocardial oxygen tension (Pm_{O_2}) in the most ischaemic area of a myocardial infarction in pigs. The control group is indicated with closed squares and the group receiving prior haemodilution with Fluosol-DA 20 % is indicated by open squares. * Significant decrease in Pm_{O_2} ($P < 0.05$).

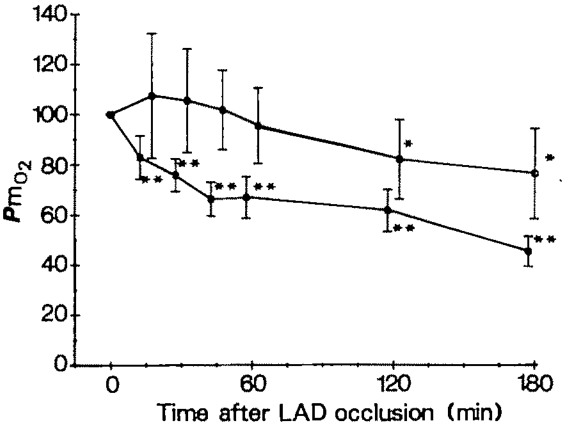

FIG. 2. Percentage changes in myocardial oxygen tension (Pm_{O_2}) in all electrodes during myocardial infarction in pigs. The control group is indicated with closed squares and the group receiving prior haemodilution with Fluosol-DA 20 % is indicated by open squares. * Significant decrease in Pm_{O_2} ($P < 0.05$).

those in the FDA group. Some individual values were quite low, and the critical oxygen delivery level Qc_{O_2} (the point below which the body could no longer maintain $\dot{V}O_2$) was calculated using the least squares method, to determine the intersection of two regression lines passing through all $\dot{V}O_2/QO_2$ data points [8, 9]. A Qc_{O_2} value of 8.2 ml min^{-1} kg^{-1} was obtained for the control animals. Although this value has no direct relationship to the present study, it is recorded because, as far as we are aware, no values for Qc_{O_2} in pigs have been published.

Initial analysis of myocardial oxygen tensions was performed on results from the microelectrode showing the greatest percentage decrease in Pm_{O_2} over the first 1 h of occlusion in each individual animal [6]. This was assumed to be in the most hypoxic area of myocardium. Figure 1 illustrates the percentage changes for this electrode in the control and FDA groups (statistical analyses were performed on the actual measured values). Although Pm_{O_2} had decreased significantly in the control group 15 min after LAD occlusion, this was not significantly less than the pre-occlusion values in the FDA-diluted group until 45 min of ischaemia had elapsed. At all times mean changes were less in the FDA group.

Percentage changes for all electrodes are shown in figure 2. Pm_{O_2} was significantly lower than pre-occlusion values after 15 min of occlusion in controls, whereas this was not seen till 120 min after LAD occlusion in the FDA group. At the end of the experiments Pm_{O_2} values in the FDA group were significantly higher than in the control group.

DISCUSSION

Previous work in pigs [6,10] has demonstrated that haemodilution with Fluosol-DA 20%, in the same volumes as used in this study, could materially affect Pm_{O_2} if performed 1 h after occlusion of the lower one-third of the LAD. At the end of the haemodilution procedure, Pm_{O_2} in the most ischaemic area was no longer significantly different from pre-occlusion values. Three hours after haemodilution, mean values of Pm_{O_2} were only 7.8% below pre-occlusion values. At this time values of Pm_{O_2} in dextran-diluted animals and control animals were reduced 60.3% and 72.2%, respectively.

The present study indicates that, although prior haemodilution with FDA cannot completely prevent decreases in Pm_{O_2} in this model, the changes can be reduced substantially and delayed in onset. In a clinical situation both of these effects would be beneficial.

It could be argued that many of the effects of treatment with FDA were the result of simple haemodilution. This would tend to be confirmed by the increases in cardiac output and the decreases in peripheral vascular resistance in this group. However, haemodilution with crystalloid solutions does not decrease subsequent myocardial ischaemia as assessed by elevation of the ST segment [11]. Pre-ischaemic haemodilution with colloidal dextran was shown by Cohn and colleagues [12] to lessen subsequent ST elevation, but the observations were not continued beyond 20 min of ischaemia. The significance of these findings is open to question, as no details of cardiac work were reported and it is quite possible that oxygen supply/demand kinetics were dissimilar in the different groups.

Post-ischaemic haemodilution with dextran solutions has not been shown to improve myocardial ischaemia as assessed by flow to ischaemic areas [12], infarct size [13], Pm_{O_2} [6] or oxygen delivery [14]. For the above reasons, and because of our desire to compare haemodilution with FDA with the "normal" untreated condition, the control group was not haemodiluted. In the present experiments, pre-ischaemic Pm_{O_2} values were not significantly different in the two groups and this further suggests that myocardial oxygenation was unaffected by haemodilution with FDA.

The use of halothane as the anaesthetic in these studies might be criticized because this (and many other anaesthetic agents) can be detected by polarography. Errors in oxygen measurement when halothane was used have been investigated and it was concluded that, at the low concentrations used during anaesthesia, these were probably small in most instances [15]. Indeed, in the presence of a constant concentration of a second polarographically detectable substance in the tissues (halothane), the relative changes of the primarily detected substance (oxygen) may actually be underestimated [6].

FDA can beneficially affect a number of tissues subjected to ischaemic hypoxia. It lessens cerebral hypoxic damage [16], particularly when administered with mannitol before ischaemia [17]. Subarachnoid space perfusion with oxygenated fluorocarbon nutrient solution also caused marked improvement following severe global cerebral ischaemia [18] or spinal cord injury [19]. Clinically, Fluosol perfused during balloon angioplasty of coronary arteries successfully reduced electrocardiographic signs of myocardial hypoxia [20]. The agent has also been used for "resuscitation" of traumatically amputated human extremities, which were later reimplanted successfully [21].

The mechanism by which FDA exerts a protective effect in the presence of hypoxia or diminishes reperfusion damage [22] is unclear, and a number of hypotheses have been put forward.

Perfluorocarbon (PFC) emulsions have a very low viscosity which, unlike that of blood, hardly alters as shear rate decreases in the microcirculation [23]. This implies a higher tissue blood flow for the same transcapillary pressure and, under conditions limiting oxygen flux, improved tissue oxygenation. This view was taken by Biro [24], who suggested that reduction in viscosity by haemodilution might improve perfusion through available collaterals. However, it has been shown recently [25] that, under conditions of extreme haemodilution, *in vivo* viscosity may actually increase. This was attributed to margination of PFC particles and increase in frictional resistance to red cell transit through capillaries. This effect would be greater in high flow microshunts and, hence, proportionately less shunt perfusion and better matching of supply and demand would occur.

Kloner and Golgar [26] have maintained that the small PFC particles may bypass obstructions in the circulation caused by endothelial blebs and sludged red cells. Others [21,27] have maintained that the particles can penetrate deep into hypoxic tissue beds, not only bypassing sludged cells, but reoxygenating them and reversing the red cell membrane stiffening that occurs under conditions of hypoxia and acidosis [28]. Hence, the vicious circle of sludged standstill can be broken.

Whatever the mechanism of improvement of oxygenation of ischaemically hypoxic tissues, there is little doubt that PFC emulsions are effective in this respect and recent work [9] has shown that haemodilution with FDA can substantially increase oxygen extraction and decrease critical values of oxygen delivery during progressive haemorrhagic shock, even when breathing ambient air. It has been suggested that this is not only the result of improved microcirculatory perfusion, but may also result from improved diffusion of oxygen from the red cell into the tissues [29].

PFC may also affect the ultimate outcome of ischaemic hypoxia, particularly where revascularization procedures have been carried out, by their actions on leucocytes. Virmani and co-workers [30, 31] have demonstrated that Fluosol-DA can inhibit neutrophil phagocytosis, chemotaxis and superoxide release. These actions help explain the decreased inflammatory response and increased myocardial salvage observed following early post-infarction haemodilution with PFC [5] and the ability of these compounds to protect against the reperfusion syndrome [22, 32].

It has now become clear [33, 34] that, if FDA is used in the treatment of acute myocardial ischaemia, a certain length of time is necessary before it exerts a beneficial effect. In the present study, occlusion of the terminal LAD was performed within about 30 min of the completion of haemodilution with FDA. It is unclear if there is an optimum period before vascular occlusion during which these procedures should be carried out. If the time necessary for therapeutic effect is dictated by the gradual restoration of the normal flexibility of the erythrocyte membrane, it is unlikely that the administration of Fluosol far in advance of the ischaemic episode would demonstrate any therapeutic gain.

No compensatory increases in Pm_{O_2} are to be seen in the border areas of acute myocardial infarction in pigs [35]. These would be expected if compensatory vasodilatation were occurring [36]. In figure 2 it is quite clear that there are considerable differences in the size of the standard errors of the means in the two experimental groups. We would suggest that this is the result of large increases in microcirculatory flow in the border areas of the infarct in the FDA-diluted animals. This may partially explain the improvement in myocardial oxygenation in this group.

In conclusion, the results obtained in this study demonstrated that prior haemodilution with FDA can substantially diminish decreases in Pm_{O_2} after acute myocardial ischaemia. In untreated pigs with LAD occlusion, Pm_{O_2} is significantly decreased within 1 min in the most ischaemic areas [35] and remains so for at least the first 1 h following the induction of ischaemia. The 45-min delay in decreases in Pm_{O_2} in the most ischaemic areas in the FDA-treated animals represents a significant therapeutic gain in this group and, in a clinical situation, would probably be adequate to allow myocardial revascularization procedures to be instituted. The degree of permanent myocardial damage could then be decreased.

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MAGNESIUM AND CORONARY REVASCULARIZATION

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SUMMARY

Twenty patients, who underwent coronary revascularization without cardioplegic arrest, were given (during cardiopulmonary bypass) either magnesium chloride 16 mmol in 10 ml of water (magnesium group) or 10 ml of water alone (control group). Plasma and urinary magnesium concentrations were measured for 24 h after operation. ECG was recorded continuously during this period. QT intervals corrected for heart rate (QT_{corr}) were calculated from periodic full lead ECG. The mean plasma magnesium concentrations in the control group were less than normal throughout the study, while hypomagnesaemia did not occur in the magnesium group. Urinary magnesium excretion was higher in the magnesium group, with 58% of the administered magnesium excreted in the first 24 h. The observed incidence of frequent or ventricular arrhythmias was 22% in the magnesium group compared with 63% in the control group. No significant differences in QT_{corr} intervals were observed between the groups.

Hypomagnesaemia affects the cardiovascular system in a number of ways. Coronary artery spasm has been observed in animals [1, 2] and an increased incidence of arrhythmia has been reported in man [3, 4]. Hypomagnesaemia enhances digitalis-related arrhythmias [5] and has been associated with sudden death in patients with ischaemic heart disease [6]. The magnesium content of myocardial muscle has been found to be low following myocardial ischaemia [7–9], while the administration of magnesium i.v. following acute myocardial infarction has been shown to reduce the incidences of arrhythmia and mortality [10]. In patients undergoing mitral valve replacement, who had received chronic diuretic therapy and exhibited increased QT_{corr} intervals on their ECG, preoperative treatment with magnesium by mouth reduced the incidence of postoperative arrhythmia [11].

Previous studies have shown a decrease in plasma magnesium concentration in association with extracorporeal haemodilution [12]. This can be prevented by using magnesium-containing solutions to achieve cardioplegic arrest [13]. The present study examines the effect of the intraoperative administration of magnesium chloride 16 mmol on plasma magnesium concentration after coronary revascularization without cardioplegic arrest. QT intervals corrected for heart rate (QT_{corr}) and the frequency of ventricular arrhythmias, were examined in magnesium-treated and control groups.

PATIENTS AND METHOD

Twenty patients underwent coronary artery bypass grafting, which was performed during intermittment aortic cross-clamping and induced ventricular fibrillation at 32 °C. On the day before surgery, baseline measurements of plasma magnesium, serum potassium, calcium and creatinine kinase (MB fraction) concentrations were obtained and a 12-lead electrocardiogram with derived measurements of QT_{corr} interval was recorded. Patients with preoperative plasma magnesium concentrations outside the reference range (0.74–0.99 mmol litre^{-1}), or those receiving chronic diuretic or specific anti-arrhythmic therapy were excluded. All patients received their normal therapy of beta-adrenergic, calcium antagonist, or both, on the day of operation.

Patients were allocated randomly to receive either magnesium chloride 16 mmol in 10 ml water or placebo (water 10 ml) in a coded ampoule, which was injected to the venous side of

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the extracorporeal circuit during the first aortic cross-clamp period of cardiopulmonary bypass. The dose of magnesium corresponds to that in one ampoule of St Thomas's Hospital cardioplegic solution. Frusemide 20 mg was given concomitantly, in keeping with routine clinical practice.

The quantities of calcium and potassium and all other drugs, and the volumes of fluids, administered during the study period were recorded. The anaesthetic and postoperative management were similar for all patients, and involved immediate extubation and management in a general surgical recovery ward, as previously described [14].

Plasma magnesium and potassium concentrations were measured before operation, at the end of bypass, on arrival in the recovery room and at 1, 2, 4, 6 and 24 h after operation. Serum calcium concentration was measured before, and at 6 and 24 h after, operation.

Urinary magnesium concentrations were measured over three periods of time: A from the first cross-clamp (during cardiopulmonary bypass) to the end of the operation, B during the first 6 h after operation and C during the next 18 h.

Magnesium concentrations in both plasma and urine were measured quantitatively by a methyl thymol-blue complexometric procedure using the DuPont ACA discrete clinical analyser. All urines were acidified before analysis. Within-run precision was 4.8% and 1.7% at magnesium concentrations of 0.96 and 8.11 mmol litre^{-1}, respectively.

Twelve-lead electrocardiography was performed before, and repeated at 6 and 24 h after surgery. QT_{corr} intervals were derived using the relationship: $QTi/\sqrt{RR}$ where QTi is the measured QT interval and RR is the time interval between adjacent R waves. Evidence of myocardial infarction was based on the appearance of new Q waves, together with an increase in creatinine kinase (MB fraction) concentration to greater than 6% of total creatinine kinase activity, when comparing a measurement at 24 h after operation with the preoperative measurement.

The electrocardiogram was recorded continuously in the postoperative period, by means of an Oxford 24-h, single-channel tape recorder for subsequent off-line analysis of heart rate and rhythm using a Reynolds Pathfinder 3 Arrhythmia Analysis System. The tapes were analysed independently before the double-blind trial code was broken. Types of arrhythmia were recorded and an assessment made of the frequency of occurrence from the cardiology department reports on the 24-h tapes using their standard classification of absent, occasional or frequent.

Statistical differences between the groups were evaluated using an unpaired Student's t test and comparisons in the same individual with the paired t test.

RESULTS

Nine of the 20 patients in the study were given magnesium chloride, and 11 acted as controls. There were no significant differences between the groups with regard to age, body surface area, preoperative ejection fraction, number of distal coronary anastamoses, duration of cardiopulmonary bypass, aortic cross-clamp (myo-

TABLE I. *Patient and operative data (mean ± SEM)*

	Magnesium group	Control group
Age (yr)	58.4±2.23	61.9±1.62
Body surface area (m^2)	1.90±0.02	1.90±0.05
Ejection fraction (%)	55.2±5.02	49.9±2.05
Anastamoses	3.4±0.24	3.6±0.24
Duration of bypass (min)	82.2±4.85	84.9±4.99
Cross-clamp time (min)	36.4±2.91	38.5±3.16
Urea concn (mmol litre^{-1})	5.93±0.64	6.49±0.85
Creatinine concn (mmol litre^{-1})	95.7±6.31	96.2±7.68

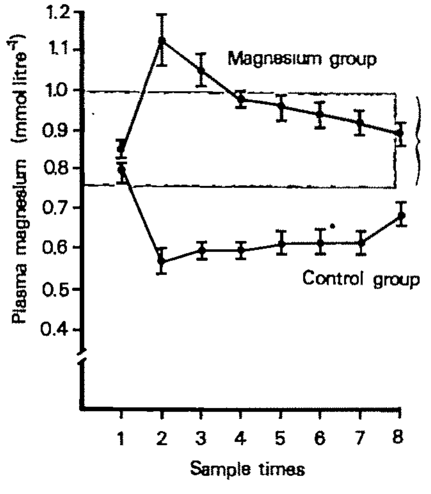

FIG. 1. Mean (±SEM) plasma magnesium concentrations. Sample times: 1 = Before operation; 2 = end of bypass; 3 = end of operation; 4 = 1 h after operation; 5 = 2 h after operation; 6 = 4 h after operation; 7 = 6 h after operation; 8 = 24 h after operation. Stippled area represents normal reference range.

TABLE II. *Mean (±SEM) values for urine volumes and urinary magnesium. A = first aortic cross-clamp to end of operation; B = first 6 h after surgery; C = subsequent 18 h*

	Magnesium group			Water group		
	A	B	C	A	B	C
Urine volume (ml)	1090±113	1470±184	1620±105	820±115	1450±178	1620±249
Urinary magnesium (mmol litre^{-1})	3.52±0.38	3.34±0.43	2.54±0.36	1.34±0.19	0.95±0.12	0.71±0.17

TABLE III. *Mean (±SEM) values for plasma potassium concentration (mmol litre^{-1})*

	Time after operation (h)					
	0	1	2	4	6	24
Magnesium group	4.58±0.19	4.41±0.20	4.89±0.13	4.65±0.23	4.80±0.18	4.56±0.14
Control group	4.28±0.11	4.05±0.08	4.82±0.14	4.61±0.20	4.66±0.11	4.52±0.18

TABLE IV. *QT_{corr} intervals (ms) (mean±SEM)*

	Magnesium group	Control group
Before operation	37.3±1.09	39.4±0.74
After operation		
6 h	41.2±0.95	39.5±1.09
24 h	41.3±1.64	38.5±0.76

cardial ischaemic) time, or preoperative urea and creatinine values (table I).

There was also no significant difference in the mean values of preoperative plasma magnesium concentrations between groups, but at all other sample times the mean values in the control group were significantly lower ($P < 0.001$) than those in the magnesium-treated group. All mean values for plasma magnesium concentration after cardiopulmonary bypass in the control group were significantly lower than the preoperative values ($P < 0.01$) and remained below the normal reference range over the study period (fig. 1). Only three patients in the control group had values greater than 0.74 mmol litre^{-1} at 24 h after surgery. In the magnesium-treated group, mean plasma magnesium concentrations were above the reference range following cardiopulmonary bypass until 1 h after operation, following which they remained within normal limits (fig. 1). Individual patients in this group, however, were hypermagnesaemic for variable periods, and one patient still had an increased plasma magnesium concentration at 24 h (1.10 mmol litre^{-1}). No patient had a plasma magnesium in excess of 1.38 mmol litre^{-1}.

There was no significant difference between the groups for mean total urine output over 24 h. Three patients in the control group required an additional frusemide 20 mg during the postoperative period. The mean urinary concentration of magnesium was significantly higher ($P < 0.01$) in each of the three time periods in the magnesium group compared with the control group (table II). Over 24 h, the control group excreted a mean total amount of magnesium 3.43 mmol compared with 12.17 mmol in the magnesium group. The difference represents 58% of the initial 16 mmol of magnesium given. I.v. fluid, calcium and potassium administration and serum calcium, and albumin concentrations were not significantly different between the groups. There were no significant differences between groups in the mean plasma potassium concentrations at any of the times it was measured in the study. Table III shows the mean plasma potassium values during the postoperative period.

Mean QT_{corr} intervals did not alter significantly from preoperative values in either group during the study and there was no significant difference between groups (table IV).

All patients were in baseline sinus rhythm after surgery. Three patients (one in the control group and two in the magnesium group) had no arrhythmia at all over 24 h. One patient in each group (both of whom exhibited frequent multifocal ventricular extrasystoles) subsequently developed atrial fibrillation and both these patients were treated with an infusion of disopyramide. Five patients in the control group (45 %) and four in the magnesium group (44 %) exhibited atrial extrasystoles. Seven patients in the control group (64 %) and two patients in the magnesium group (22 %) exhibited frequent ventricular arrhythmias (ventricular extrasystoles, couplets, bigeminy and ventricular tachycardia). This difference was significant ($P < 0.001$). One patient in the control group, who had an episode of ventricular tachycardia, was treated with a lignocaine infusion. Although exact numerical analysis of the ectopic beats or couplets could not be attempted, all patients classified as having occasional arrhythmias had less than 10 over 24 h, while all those in the frequent group were considerably in excess of this.

Three patients in each group received inotropic agents for a short period after surgery. The drugs used were isoprenaline, dobutamine and adrenaline. Two patients required all three of these inotropes. One (in the magnesium group) remained in sinus rhythm, the other (in the control group) had frequent ventricular arrhythmias. The remaining four patients, two in each group, were given isoprenaline in order to increase heart rate and all of these patients exhibited both atrial and ventricular arrhythmias. No patient had evidence of perioperative myocardial infarction on the basis of the criteria defined in this study.

DISCUSSION

This study demonstrated that patients who did not receive magnesium during non-cardioplegic cardiopulmonary bypass were hypomagnesaemic for at least 24 h after the procedure. The intraoperative administration of magnesium chloride 16 mmol produced mean plasma magnesium concentrations that lay within the normal reference range between 1 and 24 h after surgery. Although individual patients in the magnesium group were hypermagnesaemic for variable periods, none was hypomagnesaemic at any time. These observations are in keeping with two separate studies which demonstrated dilutional hypomagnesaemia during cardiopulmonary bypass [12] and hypermagnesaemia following the administration of magnesium-containing cardioplegic solutions [13].

The clinical importance of these results lies in the fact that myocardial preservation techniques, other than cardioplegic arrest, are used during coronary revascularization, in which case failure to administer magnesium to the patient could be expected to lead to postoperative hypomagnesaemia.

One of the suggested causes of hypomagnesaemia is excessive urinary loss, and there is some evidence to show that this can be appreciable [13, 15]. This study demonstrated that the total amount of magnesium excreted over the first 24 h after operation was greater in the magnesium-treated group, with the difference representing 58 % of the magnesium given during cardiopulmonary bypass. This figure is in agreement with previous work [13]. The fact that the administration of magnesium 16 mmol caused an increase in magnesium excretion over 24 h by a factor in excess of 3.5 over the control group, despite a similar diuresis, indicates that magnesium load and intraoperative haemodilution have greater influence on plasma magnesium concentration and urinary magnesium excretion than urine output *per se*.

Many different arrhythmias have been reported in association with magnesium deficiency, but ventricular tachyarrhythmias occur most frequently [3]. This may be related to the role of magnesium in the manufacture of membrane adenosine triphosphatase and, hence, maintenance of intracellular potassium [15]. Arrhythmias related to hypomagnesaemia may be refractory to any other therapy than the administration of i.v. magnesium [16].

The incidence of atrial arrhythmias was similar in the two groups. However, the incidence of frequent ventricular arrhythmias in the control group, 64 %, was nearly three times greater than that found in the magnesium-treated group. This, coupled with the fact that hypomagnesaemia is particularly associated with ventricular tachyarrhythmias, suggests that failure to administer magnesium during operation may increase the potential for the development of ventricular arrhythmias during the first 24 h after coronary revascularization. It is appreciated that the number of patients studied was small and further investigation is in progress in order to confirm the effect of the administration of magnesium on the incidence of postoperative arrhythmia.

ECG changes seen in hypomagnesaemia (prolonged PR intervals, wide QRS complexes, depressed ST segments and inverted T waves) are very similar to those seen in hypokalaemia, and both may also be associated with a prolonged QT interval [15]. Prolongation of the QT interval itself is associated with an increase in arrhythmic potential. Other causes of a prolonged QT interval include hypocalcaemia, myocardial ischaemia and antiarrhythmic therapy [17, 18]. In this study every effort was made to reduce the influence of known factors (excluding plasma magnesium) on the QT_{corr}. Thus patients on chronic anti-arrhythmic therapy were excluded from the study and new myocardial ischaemia changes were not evident in any of the patients. Serum potassium and serum calcium concentrations were monitored closely and there was no significant difference between groups with regard to these measurements. In this study, we could demonstrate no effect on the QT_{corr} interval associated with the administration of magnesium chloride during cardiopulmonary bypass, despite the wide variations in perioperative magnesium concentrations between the groups. Any arrhythmias observed in this study, therefore, occurred without electrocardiographic evidence of QT prolongation.

CONCLUSION

Following cardiopulmonary bypass without cardioplegic arrest, all control patients were found to be hypomagnesaemic for at least 24 h. Conversely, mild hypermagnesaemia in the immediate postoperative period, followed by normal plasma magnesium concentrations, were demonstrated in the first 24 h in those patients who received magnesium chloride 16 mmol during cardiopulmonary bypass. Fifty-eight percent of the magnesium given during bypass was excreted in the urine over the next 24 h, but hypomagnesaemia was not caused principally by excessive urinary loss. These observations were not associated with any significant differences in the duration of QT_{corr} between patient groups.

Patients in the control group demonstrated a nearly three-fold incidence of frequent ventricular arrhythmias compared with the magnesium-treated patients. Hypomagnesaemia may be one of the many contributory factors that predispose towards the development of postoperative arrhythmias, and the intraoperative administration of magnesium may reduce the incidence of potentially serious ventricular arrhythmias following coronary revascularization.

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ISOFLURANE AND LARGE CORONARY ARTERY HAEMODYNAMICS†

A Study in Dogs

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SUMMARY

In the dog, stepped increases in isoflurane concentration (up to 1.5 MAC) caused peripheral and coronary vasodilatation. In the presence of significant decreases in arterial pressure (−35%), contractility (−46%), cardiac output (−17%) and coronary perfusion pressure (−40%), coronary blood flow remained unchanged, while the effective coronary vascular resistance was halved. The coronary reserve, estimated by the hyperaemic response to short periods (10 s) of coronary occlusion was reduced by the stepped increases in isoflurane concentration. Linear relationships were observed between peak hyperaemic flow, volume repayment, repayment:deficit ratio and coronary perfusion pressure. The vasodilatation induced by isoflurane was of such magnitude that, at 1.5 MAC, the repayment:deficit ratio was close to unity, indicating that the vasodilatory reserve was almost exhausted.

Isoflurane is known to have marked vasodilating properties and this action also affects the coronary arteries [1–7]. These features, together with some circumstantial evidence, have given rise to the view that isoflurane may cause a coronary "steal" phenomenon [4–9]. Such a notion implies that isoflurane interferes with the normal autoregulation of coronary vascular resistance, that is, the ability to vary coronary blood flow at similar perfusion pressures in response to changing myocardial oxygen needs. In the case of a "steal" phenomenon, flow through normal coronary vessels would have to be in excess of tissue requirements and coronary vascular reserve [10] would have to be impaired.

To test the autoregulatory function, the hyperaemic response to brief coronary arterial occlusions was measured at increasing depths of isoflurane anaesthesia in the dog.

METHODS

Seven dogs of mixed breed (mean weight 24 kg ±2 kg SEM) were studied as part of a more complex study [11]. The animals were premedicated with morphine 1.5 mg kg^{-1} i.m. and anaesthesia was induced with thiopentone 15 mg kg^{-1} i.v. The trachea was intubated and controlled ventilation instituted with an inspired gas mixture of 60% oxygen in nitrogen. Normocapnia was assured by capnometry and anaesthesia was maintained during the surgical preparation with 1.5–2.0% halothane. A heating element, incorporated into the operating table, maintained body temperature between 37 °C and 38 °C, as measured by an oesophageal thermistor probe. The left carotid artery was exposed, and a rigid 7-French gauge cannula introduced and advanced into the aortic root for pressure measurement and blood sampling. Through a left lateral thoracotomy the pericardium was fashioned into a cradle to support the heart and another rigid 7-French gauge cannula was inserted into the apex of the left

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ventricle to allow high fidelity measurements of pressure. Differentiation of this signal yielded LV dP/dt. Dissection of the left anterior descending (anterior interventricular) coronary artery just distal to the origin of the first diagonal branch allowed a snare and an electromagnetic flow transducer of appropriate size to be applied. Aortic blood flow was measured using a second cuff-type electromagnetic flow transducer. Miniature ultrasonic displacement transducers were implanted in subendocardial myocardium in the territory supplied by the exposed artery and in territory supplied by the circumflex coronary artery. The technique of sonomicrometry has been reported from this laboratory in the past [12]. In this instance it was used to monitor myocardial welfare, and document the presence or absence of ischaemic dysfunction.

After completion of the surgical preparation, the anaesthetic was changed to isoflurane, a period of 60 min was allowed for stabilization at 1 MAC (determined as 1.13 % isoflurane in end-tidal gas), and the anaesthetic breathing circuit was changed. After calibration of all equipment, the animals were exposed to stepped increases in the inspired concentration of isoflurane so that, after 10 min at each concentration, a stable alveolar value had been achieved, as shown in table I.

When equilibrium conditions were achieved at each dose, an accurately-timed 10-s occlusion was applied to the exposed coronary artery. The measurements illustrated in figure 1 were recorded from the mean coronary blood flow trace: mean flow, occlusion volume deficit, peak hyperaemic flow, duration of hyperaemic response, volume repayment and the repayment: deficit ratio. Following the temporary occlusion of the LAD artery, the return of normal segmental contractile function was assured before proceeding to the next dose. At the end of the experiment, 5-ml aliquots of blood were injected into the LAD to calibrate the flow transducer.

Recordings of the occlusion and hyperaemic responses were made at a paper speed of 50 mm s^{-1}, and the areas representing the volume deficit during arterial occlusion and the volume repayment during the hyperaemic response were determined by planimetry. At the end of the investigation the territory supplied by the LAD artery was defined by the injection of Evans blue dye into the vessel at the site of the flow transducer. Careful weighing of the stained muscle allowed the calibration of mean flow recordings in ml min^{-1} per 100 g of muscle. Coronary perfusion pressure was calculated by subtracting LV end-diastolic pressure from aortic diastolic pressure, and "effective coronary vas-

TABLE I. *Sequence of alveolar isoflurane concentrations (mean ± SEM in seven dogs) and their MAC equivalent*

MAC multiples	End-tidal isoflurane concentration (%)
0.50	0.57 ± 0.01
0.75	0.85 ± 0.01
1.00	1.13 ± 0.01
1.25	1.41 ± 0.02
1.50	1.70 ± 0.02

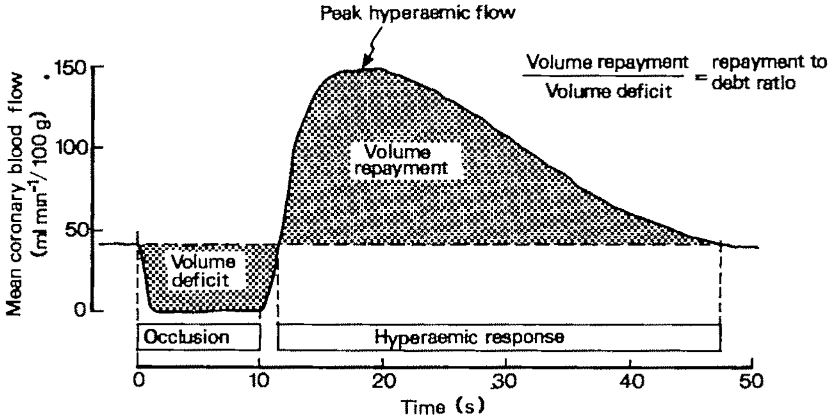

FIG. 1. Slow recording of the time course of the hyperaemic response following 10 s of occlusion of the left anterior descending coronary artery. The shaded areas represent volume deficit and volume repayment, respectively.

cular resistance" (ECVR) was calculated by dividing coronary perfusion pressure by mean flow.

The data were analysed using two-way analysis of variance and Duncan's multiple range test. Linear regression analysis was performed using the least squares method. $P < 0.05$ was considered significant; all values are given as mean ± SEM.

RESULTS

Coronary circulation (table II)

There was a dose-related reduction in effective coronary vascular resistance, so that at 1.5 MAC isoflurane, mean ECVR had decreased to 53% of the control value ($P < 0.001$). These changes indicated a significant mean reduction in coronary perfusion pressure, while coronary flow remained unchanged.

Because coronary blood flow was essentially unchanged as the isoflurane concentration was increased, the mean volume deficit was unchanged. However, peak hyperaemic flow (−51%), volume repayment (−76%), and the ratio of repayment to deficit (−78%) decreased markedly. The duration of the hyperaemic response was also significantly reduced (−49%). As illustrated in figure 2, peak hyperaemic flow and volume repayment were found to bear linear relationships to coronary perfusion pressure. However, the hyperaemic response was not abolished, as indicated by the repayment:deficit ratio of 1.0 at 1.5 MAC isoflurane.

Cardiac function

Some of the indices of global cardiovascular function recorded simultaneously with the values of coronary haemodynamics are shown in table III.

While heart rate increased significantly (+18%), peak left ventricular pressure (−33%), mean arterial pressure (−35%), LV dP/dt (−46%) and peak left ventricular power (−56%) all decreased significantly. Systemic vascular resistance decreased in a dose-dependent fashion (−20%). Cardiac output was reduced by 17% at 1.5 MAC isoflurane.

Ischaemic contractile dysfunction developed in the territory supplied by the LAD artery *during* the brief coronary artery occlusions, but dysfunction never persisted beyond the duration of the hyperaemic response. We take this to mean that any oxygen debt incurred by the occlusion had been fully repaid, and that there was no lasting ischaemia in the region.

TABLE II. *Effects of stepped increases in alveolar concentration of isoflurane on the coronary circulation in seven dogs. Means ± SEM.* *P < 0.05 *compared with the initial 0.5 MAC isoflurane values*

	MAC isoflurane					
	0.50	0.75	1.0	1.25	1.50	0.50
Coronary flow (ml min^{-1}/100 g)	40.6±4.1	39.7±4.9	39.3±4.9	42.8±7.1	41.1±7.2	41.4±3.2
Coronary perfusion pressure (mm Hg)	78.0±5.2	68.0*±4.3	62.4*±4.7	56.4*±4.6	47.0*±4.7	84.3±4.4
Coronary vascular resistance (mm Hg ml^{-1} min^{-1}/100 g)	2.00±0.23	1.70*±0.25	1.47*±0.21	1.21*±0.15	1.06*±0.15	2.11±0.08
Volume deficit (ml)	2.6±0.6	2.4±0.5	2.5±0.4	2.6±0.5	2.5±0.5	2.3±0.3
Volume repayment (ml)	10.2±1.9	7.2*±1.7	5.0*±1.7	3.7*±1.4	2.4*±1.0	8.0±1.7
Peak hyperaemic flow (ml min^{-1}/100 g)	124.5±9.4	97.7*±8.0	85.4*±8.8	77.1*±9.8	61.7*±9.3	106.9±13.4
Repayment:deficit ratio	4.6±1.1	3.7±1.1	2.1*±0.8	1.6*±0.7	1.0*±0.5	3.7±0.8
Repayment:deficit ratio (%)	100	77.9±13	50*±16	38.6*±14	26.6*±10.2	97±18.9
Duration of hyperaemia (s)	34.5±2.7	30.3±4.2	24.8*±2.8	22.7*±2.6	17.7*±3.5	30.0±3.6
$\frac{\text{Peak hyperaemic flow}}{\text{Mean flow}}$	3.2±0.3	2.6*±0.2	2.2*±0.2	1.9*±0.2	1.5*±0.2	2.7±0.3

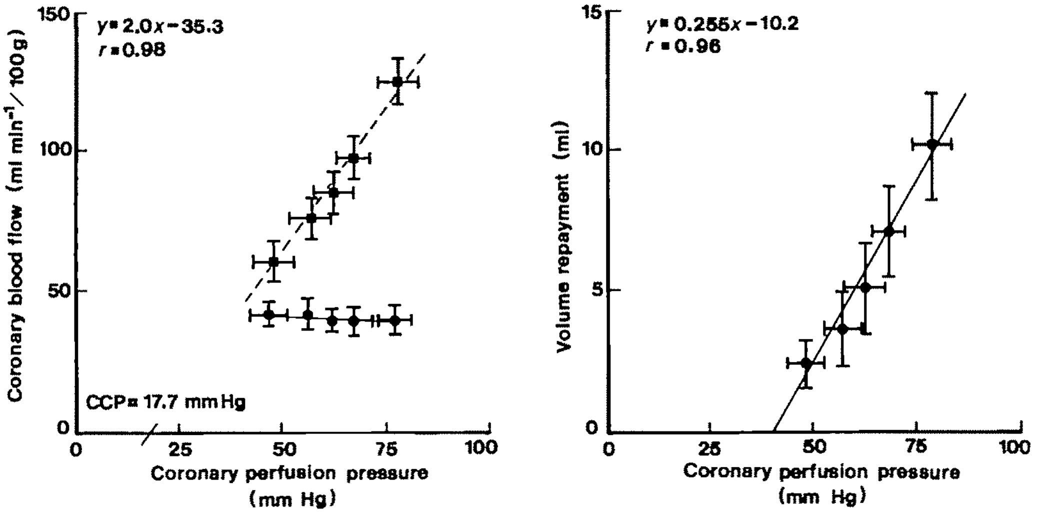

FIG. 2. Left hand panel: linear relationship observed between peak hyperaemic coronary flow (■) and coronary perfusion pressure. Each point represents mean ± SEM in 7 dogs. Before the hyperaemic response resting flow (●) was not pressure dependent. Note that the intercept of this relationship defines the critical closing pressure (CCP). Right hand panel: linear relationship between volume replacement and coronary perfusion pressure.

TABLE III. *Effects of stepped increases in alveolar concentration of isoflurane on the circulation in seven dogs. Means ± SEM.* *P < *0.05 compared with the initial 0.5 MAC isoflurane values*

	MAC isoflurane					
	0.50	0.75	1.0	1.25	1.50	0.50
Heart rate (beat min^{-1})	95.3 ± 7.5	106.7* ± 8.4	109.2* ± 10	112.7* ± 10.1	113.0* ± 9.2	110.1* ± 11.9
Mean arterial pressure (mm Hg)	96.7 ± 5.2	84.5* ± 4.6	78.2* ± 4.8	72.3* ± 4.8	62.5* ± 5.2	102.1 ± 3.6
Peak LV pressure (mm Hg)	121.8 ± 5.5	107.6* ± 5.4	99.1* ± 5.2	92.2* ± 5.5	81.9* ± 6.3	125.3 ± 3.5
LVEDP (mm Hg)	6.1 ± 0.6	5.0 ± 0.3	5.4 ± 0.4	5.9 ± 0.4	5.8 ± 0.3	5.8 ± 0.5
LV dP/dt_{max} (mm Hg s^{-1})	2093 ± 150	1796* ± 153	1579* ± 142	1410* ± 132	1144* ± 126	2146 ± 186
Peak LV power (mW)	3990 ± 397	3215* ± 338	2731* ± 342	2364* ± 318	1783* ± 263	3823 ± 425
Cardiac output (ml kg^{-1} min^{-1})	93.1 ± 9.5	97.3 ± 10.6	91.9* ± 10.8	87.7* ± 10.6	77.5* ± 10.1	96.2 ± 8.1
Systemic vascular resistance (dyn s cm^{-5})	3263 ± 350	2937 ± 353	2800* ± 326	2707* ± 326	2629* ± 354	3582 ± 382

DISCUSSION

Blood flow to all segments of the circulation is dependent on the arterial driving pressure. The relationship between coronary blood flow and arterial pressure is complicated by three additional factors: extravascular compressive forces, diastolic chamber pressures, and the effects of increased pressure on myocardial oxygen consumption. The pressure–flow relationships are also influenced by autoregulation and by the critical closing pressure [13].

Acute increases in arterial pressure and wall stress augment myocardial metabolism and coronary blood flow. Although autoregulation tends to maintain coronary blood flow when pressure increases, the increases in wall stress and oxygen demand produce coronary vasodilatation because local metabolic influences are dominant. Conversely, within limits, decreases in arterial pressure are associated with decreases in wall stress, oxygen requirements and blood flow.

Autoregulation is attenuated by any intervention which impairs the function of the smooth muscle in coronary vessels. In this study, we have confirmed that isoflurane causes coronary vasodilatation. As the isoflurane concentration was increased, all indices of myocardial oxygen demand, with the exception of a small increase in heart rate, were depressed in parallel with coronary perfusion pressure, and yet LAD coronary artery blood flow remained unchanged. Thus isoflurane caused coronary vasodilatation, as indicated by the significant and large reduction in effective coronary vascular resistance. Similar observations were reported by Tarnow and colleagues [1] from canine studies, with the additional information that coronary sinus oxygen content was increased at 1 MAC isoflurane. Our findings are in agreement with several recent experimental studies in which coronary vasodilatation was demonstrated [2,4–6]. Sill and colleagues [6] have shown that the site of vasodilatation is in the intramyocardial and not epicardial vessels. Despite this "luxury" perfusion, the capacity for further vasodilatation in response to oxygen lack was retained, as demonstrated by a mean repayment:deficit ratio that did not become inferior to unity.

While Katz and Linder [14] were the first to describe coronary reactive hyperaemia, its quantitative characteristics in dogs were determined by Coffman and Gregg in 1960 [15]. Peak hyperaemic flow is primarily dependent on minimal coronary vascular resistance (maximal vasodilatation) and the prevailing coronary driving pressure [16]; therefore, a linear relationship is observed between peak hyperaemic flow and coronary perfusion pressure. This was confirmed in the present study (fig. 2). The rate at which the reactive hyperaemia dissipates parallels the rate at which myocardial concentrations of adenosine decrease [17] and, by the end of this response, concentrations of lactate and high energy phosphates have returned to normal [18]. The repayment volume is almost always greater than the deficit volume, so that the repayment:deficit ratio is greater than unity, being of the order of 4 at high coronary perfusion pressures. In this study, the repayment:deficit ratio was 1 at 1.5 MAC isoflurane and the peak hyperaemic flow was about 150 % of resting flow. Thus over the range of isoflurane concentrations investigated, further vasodilatation occurred in response to brief periods of occlusion, indicating that local regulation was not abolished. Moreover, the restoration of normal contractile patterns in the territory supplied by the temporarily occluded vessel indicates that reserve coronary vasodilatation was enough to repay the oxygen debt. The attenuation of the hyperaemic response to coronary occlusion with deepening isoflurane anaesthesia reflected the decreases in perfusion pressure. This latter conclusion is supported by the linear relationships that were obtained by regression analyses of both peak hyperaemic flow (fig. 2) and volume repayment with coronary perfusion pressure (fig. 3). The regression coefficients were almost identical to those of Dole and co-workers [16], whose experiments were performed in a more dynamic preparation under steady-state chloralose anaesthesia with measurements of hyperaemic response under conditions of constant perfusion pressure.

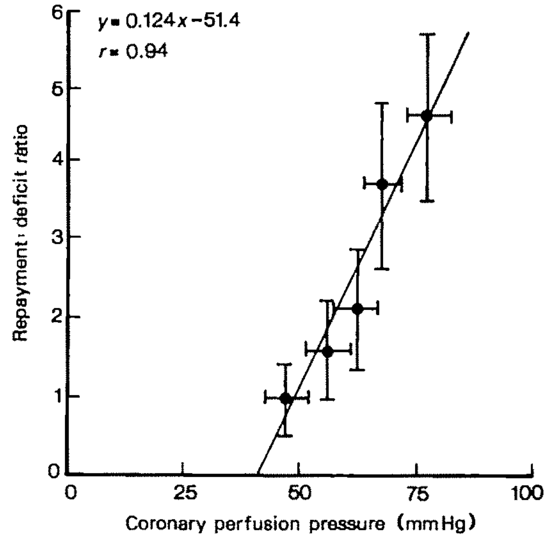

FIG. 3. A linear relationship is observed between the repayment:deficit ratio and coronary perfusion pressure. Note that at the highest isoflurane concentration tested (1.5 MAC), the ratio was close to unity.

In terms of Klocke's [10] concept of coronary vascular reserve (that is, the difference between resting coronary arterial blood flow and flow measured during maximal vasodilatation (in this case post-occlusion hyperaemia)), under the same conditions of oxygen consumption and coronary perfusion pressure, 1.5 MAC isoflurane appeared to have substantially decreased the flow reserve. However, at 1.5 MAC isoflurane *resting* flow may still have been surplus to requirements. While vasodilatation cannot be doubted, the reduction in vascular resistance may have been the result of a reduction in extravascular as well as vascular resistance [19]. Isoflurane could reduce the extravascular resistance by reducing the intramyocardial tension. The observed dose-related decreases in both systemic arterial pressure and inotropic state indicate that systolic wall tension was reduced, while isovolumic relaxation and end-diastolic pressures and dimensions remained essentially unchanged [11]. If the reduction in extravascular resistance was the major determinant of coronary vasodilatation, the critical closing pressure [13] should be low during isoflurane anaesthesia. The mean critical closing pressure, determined by extrapolation of the linear relationship between peak hyperaemic coronary blood flow and coronary perfusion pressure to the zero flow point (17.7 mm Hg) was similar to the values observed during studies of enflurane [11], and halothane anaesthesia [20]. Thus the isoflurane-induced coronary vasodilatation in normal coronary arteries is not associated with a greater decrease in coronary closing pressure than that observed with both enflurane and halothane; isoflurane does not appear to cause a greater reduction in extravascular coronary resistance than other halogenated anaesthetics.

During the studies reported by Reiz and colleagues [8,9], myocardial ischaemia occurred in patients with coronary artery disease and was attributed to a "steal" phenomenon, caused by isoflurane because of its vasodilator properties. Our canine experiments have confirmed that isoflurane causes coronary vasodilatation. We have found that the capacity for further coronary vasodilatation in response to oxygen lack is reduced, but that autoregulation is not abolished. In these circumstances, the diminution in coronary vascular reserve is directly related to the decreases in coronary perfusion pressure.

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COMPARISON OF THE EFFECTS OF ISOFLURANE OR FENTANYL–NITROUS OXIDE ANAESTHESIA ON PROPRANOLOL DISPOSITION IN DOGS

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SUMMARY

The disposition of propranolol was studied, using dual-route administration, in two groups of six dogs. Each dog was studied on three consecutive days: day 1 awake, day 2 during anaesthesia, and day 3, 24 h after anaesthesia. Anaesthesia was with isoflurane 2.0 MAC (in oxygen) in one group and with a fentanyl–nitrous oxide–atracurium regimen in the other group. In the group receiving fentanyl, anaesthesia caused a significant decrease (63%) in intrinsic clearance from the day 1 value ($P < 0.05$) and a 45% decrease in systemic clearance ($P < 0.05$). Hepatic plasma flow decreased by 27% (ns). A similar pattern was found with isoflurane: intrinsic clearance decreased by 53% ($P < 0.05$) and systemic clearance by 40% ($P < 0.05$). Hepatic plasma flow decreased by 40% (ns). In both groups, the values 24 h after anaesthesia were not significantly different from those obtained on day 1. Anaesthesia with either fentanyl–nitrous oxide–atracurium or isoflurane has a marked, but short-lasting effect on the disposition of propranolol, in part as a result of a decrease in intrinsic clearance.

Drug disposition has been shown to be altered in the period around surgery [1,2]; however, the exact nature of these changes remains unclear. Anaesthetic agents themselves might alter drug disposition by a number of mechanisms: for example by changes in the volume of distribution of a drug or in the extent of protein binding in plasma, by alterations in regional blood flow or by changes in drug metabolizing enzyme activity.

Halothane inhibits drug metabolism markedly in animals [3] and man [4]. Halothane anaesthesia in dogs has been shown to slow the elimination of propranolol [5] and verapamil [6]. However, little is known of the effect of the i.v. anaesthetic agents or opioids on drugs disposition.

For drugs metabolized by the liver, changes in drug disposition result from effects on hepatic blood flow or hepatic drug-metabolizing enzyme activity, or both. The exact nature of this effect will depend on the extent of the hepatic extraction of the drug. The clearance of a drug of high hepatic extraction given i.v. will be determined principally by its rate of delivery to the liver (that is, by the hepatic blood flow), whereas the clearance of a drug of low hepatic extraction given i.v. will be determined primarily by hepatic enzyme activity. When administered by mouth or intraportally, the clearance of drugs of both high and low hepatic extraction reflects hepatic enzyme activity and is unaffected by changes in hepatic blood flow [7]. Thus, by determining the disposition of a high extraction drug such as propranolol given simultaneously by mouth and i.v., it is possible to measure hepatic blood flow and intrinsic clearance [8–10].

In a previous study we used dual-route administration (simultaneous radio-labelled i.v. and unlabelled portal administration of propranolol) to measure the effect of halothane anaesthesia on drug disposition in the dog [5]. In the present study, using similar methods, we have compared the effects of isoflurane and

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fentanyl–nitrous oxide anaesthesia on hepatic blood flow and hepatic enzyme activity.

METHODS

Twelve male mongrel dogs were studied. Femoral artery, femoral vein and portal vein cannulae were implanted in each dog, under pentobarbitone anaesthesia (30 mg kg^{-1}) 5 days before the first study day. One group ($n = 6$, mean ± SD weight 20.7 ± 7.6 kg) received a fentanyl-based and the other ($n = 6$, mean weight 21.3 ± 7.1 kg) received an isoflurane-based anaesthetic. The disposition of propranolol was studied in each dog on three consecutive days: day 1 = 24 h before anaesthesia while awake; day 2 = during anaesthesia; day 3 = awake, 24 h after anaesthesia.

Anaesthetic regimens

In both groups, anaesthesia was induced with thiopentone 5–8 mg kg^{-1} i.v. and the trachea was intubated. The lungs were ventilated mechanically to maintain normocapnoea (Pa_{CO_2} 4.6–5.5 kPa). Intra-arterial pressure was monitored continuously throughout the study.

Fentanyl anaesthesia. Following the induction of anaesthesia, fentanyl was infused i.v., initially at a rate of 0.75 μg kg^{-1} min^{-1} for 20 min (15 μg kg^{-1} given over 20 min), and then at a rate of 0.22 μg kg^{-1} min^{-1} for the remainder of the study period. This was based on a regimen described by Murphy and Hug [11], which resulted in plasma fentanyl concentrations of approximately 8–10 ng ml^{-1}. Ventilation was with 67% nitrous oxide in oxygen. Muscle paralysis was achieved with atracurium at an initial dose of 0.3 mg kg^{-1} with subsequent doses of 0.1 mg kg^{-1} every 20 min. One hour of anaesthesia was completed before the start of the 4-h study period. At the end of the study period the infusion of fentanyl and the administration of nitrous oxide were discontinued and the dog was allowed to recover spontaneous respiration before the trachea was extubated.

Isoflurane anaesthesia. After tracheal intubation anaesthesia was maintained with isoflurane 2.0 MAC (2.3%) in oxygen. End-tidal isoflurane concentrations were measured by gas chromatography every 15 min until 2.0 MAC was obtained and then hourly until completion of the study. To allow stable haemodynamic conditions and constant end-tidal concentrations, 2 h of anaesthesia was completed before the start of the 4-h study period. The total MAC hours of volatile agent was calculated. At the end of the study the dog was allowed to recover consciousness before extubation of the trachea.

Drug disposition study

The same procedure was carried out on each of the three consecutive study days in both groups. Each dog received a bolus injection into the femoral vein of a trace dose of H^3-propranolol 200 μCi (specific activity 67 mCi mg^{-1}, Amersham Searle Corp., Arlington Heights, Il.) and, simultaneously, unlabelled propranolol 40 mg was given directly into the portal vein over 10 min by a constant rate infusion pump. The intraportal route was used to bypass the variable absorption which may occur following oral administration and which might be affected by anaesthesia.

Arterial blood samples, for measurement of both unlabelled and H^3-propranolol plasma concentrations, were obtained every 5 min for the first 1 h and then every 15 min for a further 3 h. Blood removed for sampling was replaced with twice the volume of Hartmann's solution. Plasma concentrations of unlabelled propranolol were measured by high pressure liquid chromatography and the plasma concentrations of H^3-propranolol by liquid scintillation counting of the HPLC eluent corresponding to the propranolol peak [9]. Plasma samples were obtained on each day before the propranolol was administered and the propranolol binding in plasma measured by equilibrium dialysis [12].

Systemic clearance (Cl_s), portal clearance (Cl_p), hepatic extraction ratio (E), bioavailability (F), i.v. half-life ($T_{\frac{1}{2}\text{i.v.}}$), volume of distribution (Vd) and hepatic plasma flow (Q) were calculated as described below. As propranolol is metabolized only by the liver and was injected into the portal vein (the equivalent of 100% absorption of an oral dose) the apparent clearance of the portally administered propranolol (Cl_p) is numerically equal to the total intrinsic clearance (Cl_{int}) [7].

Calculations

The clearance of propranolol following i.v. or systemic administration (Cl_s) was calculated as:

$$Cl_s = \frac{Xd_{\text{i.v.}}}{\text{AUC}_{\text{i.v.}}} \qquad (1)$$

where $Xd_{\text{i.v.}}$ is the dose of labelled propranolol administered i.v. and $\text{AUC}_{\text{i.v.}}$ is the area under the time–concentration curve calculated by the trapezoidal rule for the i.v. labelled propranolol.

The clearance of the unlabelled propranolol administered into the portal vein (Cl_p) was calculated as:

$$Cl_p = \frac{Xd_p}{AUC_p} \qquad (2)$$

where Xd_p is the dose of unlabelled drug administered into the portal vein and AUC_p is the area under the time–concentration curve for the unlabelled drug. Thus:

intrinsic clearance (Cl_{int}) = $Cl_p = Xd_p/AUC_p$

The elimination rate constant (k_{10}) was calculated by linear regression analysis and $T_{\frac{1}{2}i.v.}$ as:

$$T_{\frac{1}{2}i.v.} = \frac{0.693}{k_{10}}$$

Volume of distribution (Vd) was calculated as:

$$Vd = \frac{Cl_s}{k_{10}}$$

Hepatic plasma flow (Q) was calculated as follows:

By definition, following intraportal administration of a drug of dose (Xd_p), the amount of the drug entering the systemic circulation is equal to Xd_pF where F is the fractional systemic availability. Thus:

$$Cl_s = \frac{Xd_pF}{AUC_p} \qquad (3)$$

but, as $Xd_p/AUC_p = Cl_p$ (equation (2)), and by definition $F = 1-E$ where E is the hepatic extraction ratio:

$$Cl_s = (1-E)\,Cl_p \qquad (4)$$

Also by Fick's principle:

$$Cl_s = QE$$

where Q = apparent hepatic plasma flow.

Thus substituting for E in equation (4):

$$Q = \frac{Cl_s.Cl_p}{Cl_p - Cl_s}$$

Therefore, by substituting for Cl_p and Cl_s:

$$\text{Hepatic plasma flow} = \frac{Xd_{i.v.}.Xd_p}{AUC_{i.v.}Xd_p - AUC_pXd_{i.v.}}$$

Statistical analysis

Statistical comparisons were performed using analysis of variance followed by Student's *t* test for paired data, where appropriate. The minimal accepted level of significance was taken as $P < 0.05$. Data are given as mean ± SEM.

RESULTS

In the fentanyl study, the mean duration of anaesthesia was 5.38 ± 0.08 h. Mean total doses of fentanyl 1565 ± 150 µg and atracurium 73.0 ± 6.5 mg were administered. In the isoflurane study a mean of 11.2 ± 0.8 MAC hours of isoflurane was given.

Fentanyl study

The effects of fentanyl–nitrous oxide anaesthesia (plus atracurium-induced myoneural blockade) on the disposition of propranolol are shown in table I. The clearance of the intraportally administered unlabelled propranolol decreased significantly ($P < 0.05$) from a mean value on day 1 of 1775.2 ± 384.6 ml min^{-1} to 663.6 ± 94.7 ml min^{-1} on day 2. On day 3 (24 h after anaesthesia) the mean portal clearance of 1648.9 ± 445.0 ml min^{-1} was not significantly different from the pre-anaesthetic value. The decrease of 63% in the portal or intrinsic clearance was the result of a reduction in hepatic drug metabolizing ability which was reflected in the decrease in hepatic extraction (E) from 0.61 on day 1 to 0.46 on day 2.

There was a significant ($P < 0.05$), but smaller, decrease of 35% in the i.v. or systemic clearance of the labelled propranolol from 535.5 ± 29.2 ml min^{-1} on day 1 to 346.9 ± 41.0 ml min^{-1} on day 2. The systemic clearance measured on day 3 was not significantly different from that on day 1. As the volume of distribution was unchanged during the three study days, the change in systemic clearance is reflected by the significant increase in the i.v. half-life from 64.5 ± 6.4 min on day 1 to

TABLE I. *Effect of fentanyl on propranolol disposition in six dogs (mean values ± SEM).* * *Significantly different* ($P < 0.05$) *compared with day 1*

	Intrinsic clearance (ml min^{-1})	Systemic clearance (ml min^{-1})	I.v. half-life (min)	Hepatic plasma flow (ml min^{-1})	Volume of distribution (litre)
Day 1	1775 ± 385	536 ± 29	65 ± 6	1044 ± 233	50 ± 6
Day 2	664* ± 95	347* ± 41	98* ± 9	762 ± 99	48 ± 5
Day 3	1649 ± 445	615 ± 84	65 ± 4	1253 ± 194	56 ± 6

TABLE II. *Effect of isoflurane anaesthesia on propranolol disposition in six dogs (mean values ± SEM). Significantly different compared with day 1*: *P < *0.05*; **P = *0.053*

	Intrinsic clearance (ml min^{-1})	Systemic clearance (ml min^{-1})	I.v. half-life (min)	Hepatic plasma flow (ml min^{-1})	Volume of distribution (litre)
Day 1	1552 ± 210	479 ± 50	69 ± 7	884 ± 304	49 ± 10
Day 2	723* ± 50	286* ± 41	172* ± 43	506 ± 96	60** ± 7
Day 3	1853 ± 556	454 ± 51	85* ± 9	721 ± 79	55 ± 8

97.9 ± 9.2 min on day 2. This returned to the pre-anaesthetic value on day 3.

The hepatic plasma flow showed a non-significant decrease of 27% from 1044.1 ± 233.4 ml min^{-1} on day 1 to 762.2 ± 98.5 ml min^{-1} on day 2.

During anaesthesia the free fraction of propranolol in plasma increased from 7.0 ± 0.8% on day 1 to 8.4 ± 0.6% on day 2 ($P < 0.05$) returning toward control value on day 3 (7.8 ± 0.7%).

Isoflurane study

The effects of isoflurane anaesthesia on propranolol disposition are shown in table II. The intrinsic clearance of propranolol decreased significantly ($P < 0.05$) from 1552 ± 210 ml min^{-1} on day 1 to 723 ± 50 ml min^{-1} on day 2 (a decrease of more than 50%). This returned to 1852 ± 556 ml min^{-1} on day 3. The hepatic extraction ratio decreased from 0.66 on day 1 to 0.61 on day 2.

The systemic clearance of the labelled propranolol decreased significantly from 479 ± 60 ml min^{-1} on day 1 to 286 ± 41 ml min^{-1} on day 2 (a decrease of 40%) and returned towards control value (454 ± 51 ml min^{-1}) on day 3. As there was no change in the volume of distribution, the change in clearance resulted in a significant increase in the i.v. half-life from the day 1 value of 68.5 ± 6.7 min to 171.6 ± 42.5 min on day 2 and 84.6 ± 8.9 min on day 3.

Hepatic plasma flow was decreased (but not significantly) from 884 ± 304 ml min^{-1} on day 1 to 506 ± 96 ml min^{-1} on day 2 and 720 ± 79 ml min^{-1} on day 3. There was no significant change in propranolol plasma binding during the isoflurane study.

DISCUSSION

The disposition of propranolol was altered markedly during both isoflurane, and fentanyl–nitrous oxide–atracurium, anaesthesia. The portal or intrinsic clearance of propranolol, which is a reflection of hepatic enzyme metabolizing capacity, decreased by over 50% during anaesthesia in both studies. The extent of inhibition was similar to that seen previously with halothane [5]. In addition, using a similar experimental design, we have shown that enflurane anaesthesia also resulted in a marked inhibition of drug metabolism in the dog [13]. However, enzyme inhibition after halothane anaesthesia lasted for more than 24 h, while the effects of the anaesthetic regimens studied in the present investigation were shorter, and drug disposition had returned to pre-anaesthetic values by 24 h.

In this study, plasma propranolol concentrations were measured which, with a blood-to-plasma ratio for propranolol in the dog of 0.9, are slightly higher than blood concentrations. Thus the hepatic flow measured by this technique approximates to hepatic blood flow. The decrease in measured hepatic blood flow is of a magnitude similar to that found in other studies during anaesthesia (in the absence of surgery) with inhalation agents [14–16], and with subarachnoid anaesthesia [17]. Beta-adrenoceptor blockade is known to influence hepatic blood flow and has been shown to cause a decrease of up to 20% [18]. However, in this study, plasma propranolol concentrations were sufficient to cause near maximal beta-blockade on all three days. The increase in propranolol concentrations during anaesthesia would not explain the decrease in hepatic plasma flow that occurred during anaesthesia.

The cause of the marked decrease in hepatic drug metabolism during anaesthesia is not immediately clear, but several possible mechanisms may be considered. The inhalation anaesthetic agents may inhibit directly the cytochrome P-450 enzyme system, as has been demonstrated *in vitro* for halothane [19,20]. Isoflurane has been shown to have an inhibitory effect on oxidative metabolism, but possibly to a lesser extent than halothane [3,21]. In dogs the only significant non-oxidation pathway of propranolol metabolism is glucuronidation, which accounts for 16% of the dose [22]. Even if glucuronidation were completely blocked, it could not account for the large reduction in clearance found in this study. Anaesthesia-induced changes in hepatic blood flow may alter drug disposition [23]. Anaesthesia and controlled ventilation of the lungs *per se* may alter drug metabolizing ability. In support of this suggestion is the finding that the changes in drug disposition produced during isoflurane, fentanyl–nitrous oxide–atracurium, halothane or enflurane anaesthesia were similar. Our study did use nitrous oxide (in the fentanyl group), which does cause a small decrease in hepatic blood flow [24], and further studies are required to determine whether an i.v. anaesthetic technique without nitrous oxide has a similar effect. However, halothane anaesthesia produced an effect which was still present 24 h after anaesthesia, when all others had returned to pre-anaesthetic values.

Hypoxia may have important effects on drug metabolism [25] and antipyrine clearance (a measure of drug metabolizing ability) is related linearly to oxygen delivery and consumption [26]. In the isolated perfused rat liver the elimination of propranolol is reduced during hypoxia, a result consistent with reduced activity of the mixed function oxidase system [25]. It is possible that anaesthesia results in a relative intrahepatic hypoxia, which then produces inhibition of the mixed function oxidase system which is responsible for the biotransformation of a wide variety of drugs.

In conclusion, anaesthesia with fentanyl–nitrous oxide–atracurium or isoflurane produced a marked, but short-lasting alteration in drug disposition, in part as a result of the inhibition of drug metabolizing enzyme activity. This alteration in drug metabolism may result in considerable increases in plasma drug concentrations.

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CARDIOVASCULAR ACTIONS OF TRIMETAPHAN NITROPRUSSIDE

Comparison with Sodium Nitroprusside in Greyhounds

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SUMMARY

Trimetaphan nitroprusside (TNP) is a new potent hypotensive agent developed to induce and maintain decreases in arterial pressure unaccompanied by resistance. This study investigated its properties and compared them with those of sodium nitroprusside (SNP) in anaesthetized greyhounds. The mean dose response to TNP was obtained by measuring haemodynamic changes in five dogs. With increasing doses, stepwise decreases in mean arterial pressure and progressive increases in heart rate occurred: cardiac index did not change significantly. In a further six greyhounds, SNP and TNP were alternately infused to induce and maintain a 30% reduction in arterial pressure for 30 min. Both drugs were short-acting, decreased systemic vascular resistance and caused tachycardia. Infusion of TNP produced lower plasma and red cell cyanide concentrations; SNP maintained hypotension with significantly less tachycardia. We conclude that there was no outstanding advantage of TNP over SNP when given as a short-term infusion in greyhounds.

Sodium nitroprusside (SNP) remains one of the most popular, short-acting hypotensive agents for use in intensive care and anaesthesia. Despite its potency, resistance to hypotension may occur in young healthy subjects as a result of compensatory haemodynamic mechanisms [1]. Successful control of arterial pressure may, therefore, only be achieved either by using high doses of SNP, with the accompanying risk of cyanide toxicity [1, 2], or by the addition of agents such as beta-adrenoceptor blocking drugs [1, 3]. Trimetaphan is a vasodilator and blocker of autonomic ganglia which also suppresses the renin–angiotensin response [4, 5]. Unfortunately, it is less evanescent than SNP and elicits progressive resistance [6].

The combination of SNP and trimetaphan can produce satisfactory control of arterial pressure without the disadvantage of reflex increases in cardiac output [7], and with correspondingly lower doses of nitroprusside and blood cyanide (HCN) concentrations [8].

Trimetaphan nitroprusside (TNP) is a new compound that combines one ion of nitroprusside with two of trimetaphan to form a stable molecule. The aim of this study was twofold: to determine the dose–response and haemodynamic effects of TNP, and to establish whether TNP has any advantage over SNP under equi-hypotensive conditions in a greyhound model.

METHODS

General procedure

Healthy greyhounds were starved overnight, but had free access to water. Anaesthesia was induced with thiopentone 20–25 mg kg^{-1} i.v. and maintained with alpha-chloralose (initial bolus dose 40 mg kg^{-1}, then 10 mg kg^{-1} every 2 h) and phenoperidine (initial bolus dose 1 mg, then infused i.v. at 1 mg h^{-1}). Intubation of the trachea immediately followed induction and the lungs were mechanically ventilated with 70% nitrous oxide in oxygen. Adequate fluid balance was ensured by an infusion of 5% dextrose in 0.9% saline 4 ml kg^{-1} h^{-1}, and normothermia was maintained using a heating blanket.

Arterial pressure was measured directly from the femoral artery. A flow-directed thermo-

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dilution catheter was used to measure pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac output and temperature. Cardiac index, stroke volume index, systemic vascular resistance index and pulmonary vascular resistance index were determined using standard formulae (see Appendix). Left ventricular dP/dt_{max} was measured with a pig-tailed catheter placed in the left ventricle. All cardiovascular variables were recorded by means of an Ormed MT6 recorder. Acid–base balance and blood-gas tensions were measured at 10-min intervals during the hypotensive period. Sixty minutes after instrumentation, two baseline sets of measurements were taken to ensure haemodynamic stability.

Solutions of SNP and TNP were prepared in 5 % dextrose in 50-ml foil-wrapped syringes and infused from a Vickers infusion pump. The precise timing of the entry and exit of the drug was controlled by first infusing it through an externally primed 16-gauge cannula and then inserting and removing this at will through a shorter 14-gauge cannula placed in the external jugular vein.

Dose–response study

A TNP infusion lasting 50 min was administered to five dogs to determine the dose response. The rate of the infusion was increased step wise at 10-min intervals (1, 2.5, 5, 10 and 20 µg kg^{-1} min^{-1}). Measurements of cardiovascular function and blood-gas tensions were recorded before the end of each 10-min infusion period when haemodynamic equilibrium had been established. In two dogs the infusion of TNP was repeated after a period of 2 h to ascertain whether the first infusion affected the response to the second.

Comparison of SNP and TNP under equi-hypotensive conditions

In a randomised within-dog comparison, SNP and TNP were alternately infused to produce equi-hypotensive conditions. Three dogs received TNP first and SNP second; a further three dogs received the drugs in the reverse order. Each drug reduced the mean arterial pressure by 30 % within the first 10 min and thereafter doses were adjusted to maintain this degree of hypotension for a further 20 min. Two hours always elapsed between each infusion. Subsequent comparison included the doses of drugs used, HCN concentrations measured, and the cardiovascular effects observed. Following the discontinuation of the infusion, the times taken for the heart rate and arterial pressure to return to baseline values (±10 %) were recorded.

The total dose (nmol kg^{-1}) of the drugs given over 30 min and the mean dose rate (nmol kg^{-1} min^{-}) over the last 20 min of hypotension were calculated (molecular weight of TNP = 956). Plasma and red cell HCN, together with whole blood lactate concentrations, were measured in 15-ml and 0.5-ml arterial blood samples,

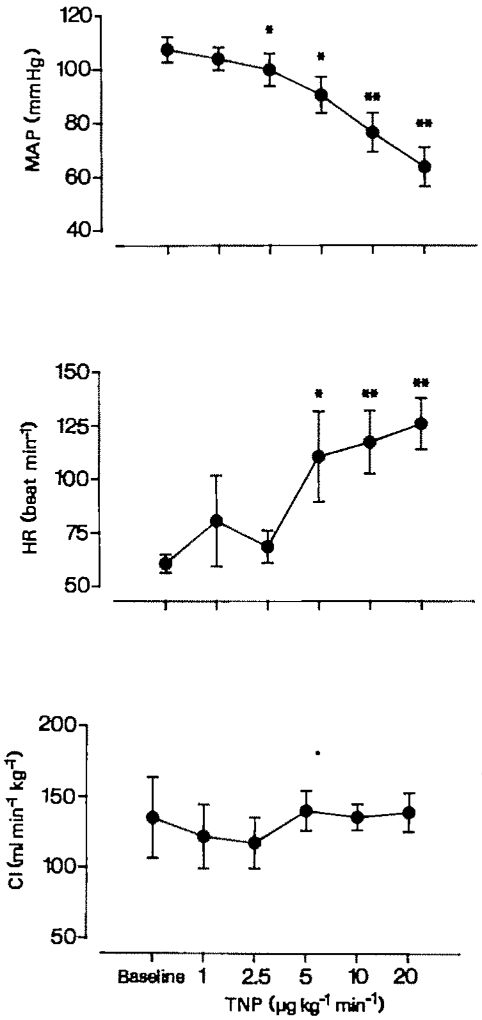

FIG. 1. Results of dose–response study. Mean arterial pressure (MAP), heart rate (HR) and cardiac index (CI) from five greyhounds (mean ± SEM) taken before (baseline) and at equilibrium during infusions of TNP. Each infusion rate (1, 2.5, 5, 10 and 20 µg kg^{-1} min^{-1}) lasted 10 min. Significant differences from baseline: *$P < 0.05$; **$P < 0.01$.

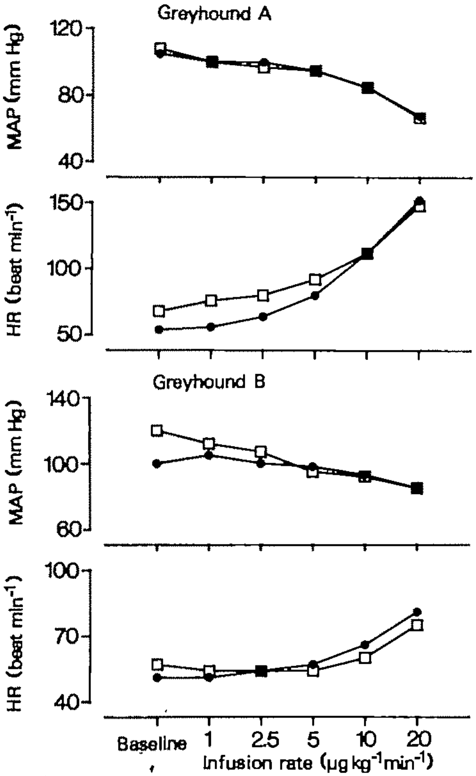

FIG. 2. Changes in mean arterial pressure (MAP) and heart rate (HR) in two dogs (A and B) taken before (baseline) and at equlibrium during two 30-min infusions of TNP. Each infusion rate (1, 2.5, 5, 10 and 20 µg kg^{-1} min^{-1}) lasted 10 min. ● = a.m. infusion; □ = p.m. infusion, following a 2-h rest.

respectively, which were taken at baseline and at the end of each infusion. Whole blood lactate concentration was determined using a fully enzymatic procedure (Boeringer Corp. Ltd), and HCN concentration by a previously described method [2, 9].

All data were normally distributed except for mean arterial pressure, drug doses, HCN concentrations and central venous pressures which were subsequently found to hold log skewed normal distributions. Student's *t* tests (paired and unpaired) were, therefore, applied and statistical significance inferred when $P < 0.05$.

RESULTS

Dose–response study

The dose response to TNP (fig. 1) demonstrated a predictable stepwise decrease in mean arterial pressure. In addition, there was a significant increase in heart rate but, overall, no change in cardiac index. When the dose responses for TNP were repeated in two dogs after a 2-h rest, the haemodynamic changes were almost identical (fig. 2).

Comparison of SNP and TNP under equihypotensive conditions

A 30% reduction in mean arterial pressure was easily obtained by SNP and TNP in each

TABLE I. *Haemodynamic measurements taken at baseline (mean ± SEM) and times after start of infusion of SNP and TNP. *Significant change from baseline*: $P < 0.05$

	Time (min)	Mean arterial pressure (mm Hg)	Heart rate (beat min^{-1})	Cardiac index (ml min^{-1} kg^{-1})	Systemic vascular resistance index (mm Hg ml^{-1} min kg^{-1})	Mean pulmonary artery pressure (mm Hg)	Pulmonary artery occlusion pressure (mm Hg)
SNP	Baseline	106	75	119	1.16	11.3	4.3
		±9.9	±5.6	±9.6	±0.14	±0.99	±0.95
	10	74*	116*	152*	0.64*	10.3	0.7*
		±6.3	±10.5	±16.4	±0.07	±0.84	±0.67
	20	73*	121*	155*	0.61*	9.8	0.2
		±6.1	±8.6	±14.4	±0.05	±0.75	±0.48
	30	73*	125*	166*	0.58*	10	0.3*
		±6.4	±10.6	±14.9	±0.06	±0.86	±0.21
TNP	Baseline	107	80	115	1.28	12.8	5.5
		±9.5	±8.5	±16.2	±0.17	±1.42	±1.34
	10	72*	143*	168	0.58*	12.3	1.3*
		±6.2	±17	±24.9	±0.05	±1.91	±0.95
	20	73*	154*	150	0.64*	11.3*	0.8*
		±6.3	±15.6	±18.3	±0.05	±1.28	±1.01
	30	74*	155*	151	0.64*	10.8*	0.0*
		±6.6	±16.3	±14.9	±0.07	±1.45	±1.0

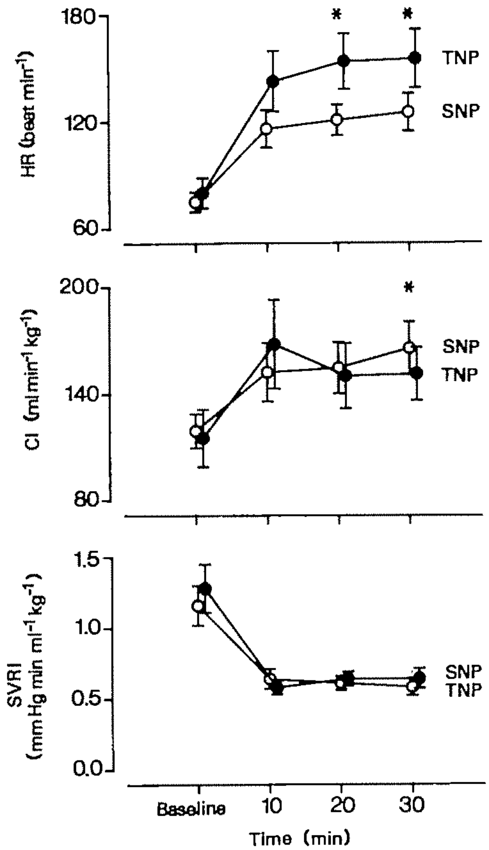

FIG. 3. Measurements of heart rate (HR), cardiac index (CI) and systemic vascular resistance index (SVRI) (mean ± SEM), obtained at baseline and at 10, 20 and 30 min after starting infusions of SNP and TNP. Significant differences between the drugs within the same greyhound: $*P < 0.05$; $**P < 0.01$.

greyhound. No significant differences were found between the first and second infusions of either SNP or TNP in drug doses, blood HCN concentrations, cardiac index or heart rate.

The haemodynamic effects of TNP and SNP were then compared with their own baseline values (table I). Both drugs significantly increased the heart rate and decreased systemic vascular resistance index and pulmonary artery occlusion pressure. Each drug increased cardiac index, but only the change produced by SNP achieved statistical significance. Although both drugs decreased pulmonary artery pressure, this was significant only following TNP. Corresponding decreases in pulmonary vascular resistance index were significant only for SNP. Small but non-significant increases in left ventricular dP/dt_{max} were seen for both drugs. Plasma lactate concentrations and blood-gas values remained within their normal ranges throughout each experiment.

Within-subject comparisons of SNP and TNP showed that SNP caused a significantly greater increase in cardiac index at 30 min, but the heart rate was clearly higher during the infusion of TNP at 20 and 30 min (fig. 3). There were no significant differences between the drugs for systemic and pulmonary vascular resistance indices. Mean pulmonary artery pressure, pulmonary artery occlusion and central venous pressures were also similar.

At the end of the infusions mean arterial pressure returned more rapidly after TNP (mean times: TNP 2.8 min, SNP 8.3 min), although heart rate took longer to reach baseline values (mean times: TNP 14.2 min, SNP 6.8 min).

Higher molar doses of SNP were required to achieve equi-hypotensive conditions, but this did not achieve statistical significance (fig. 4). Nevertheless, the plasma and red cell HCN concentrations were significantly higher after SNP ($P = 0.007$ and $P = 0.047$, respectively) (fig. 4).

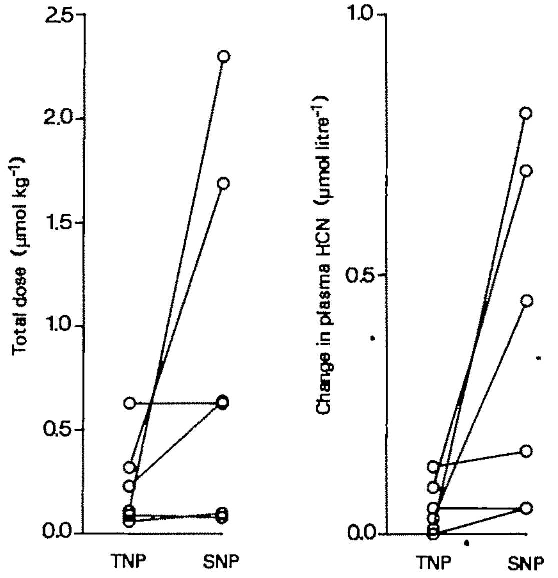

FIG. 4. Total doses of SNP and TNP used to decrease the mean arterial pressure by 30% over 30 min (see methods) in each dog (left graph). Increases in plasma concentrations of cyanide (HCN) at the end of infusion of SNP and TNP in each dog (right graph). Paired t test: $P = 0.084$ for dose comparison; $P = 0.007$ for comparison of plasma HCN concentrations.

DISCUSSION

The effectiveness of sodium nitroprusside and other potent vasodilator drugs is frequently reduced by reflex increases in heart rate and cardiac output [10, 11] with an associated increase in plasma catecholamine concentrations [5]. These compensatory mechanisms are usually undesirable in patients receiving either critical care or anaesthesia. The addition of beta-adrenoceptor blocking drugs may resolve this problem, but they are not short-acting and may compromise cardiac output and induce bronchospasm [12]. As an alternative to SNP, trimetaphan has a slower onset of effect, but the advantage of inhibiting sympathetic activation [5]. However, resistance to its action may occur [6] and return to normotension is often delayed [4]. The technique of combining SNP with trimetaphan was introduced by MacRae, Wildsmith and Dale [13], who mixed the two drugs in a weight ratio of 10:1, which corresponds to a molar ratio of 5:1. The administration of this mixture to anaesthetized patients considerably reduced the usual dose of either drug, and hypotension was achieved without a significant increase in cardiac output [7]. These findings have been confirmed by Fahmy [8] who found, in addition, that blood HCN concentrations were lower in patients receiving the mixture compared with those receiving SNP alone.

Trimetaphan nitroprusside is a compound manufactured solely for experimental trials. The lyophilized drug is a semihydrate which should be stored in the dark at a temperature of 0–5 °C. Forty milligrams of the drug is dissolved in 3 ml of 75 % ethanol and subsequently diluted with at least 50 ml of normal saline or 5 % glucose solutions and protected from light.

In this trial, we chose to compare TNP with SNP in greyhounds because they have cardiovascular systems capable of powerful compensatory mechanisms and so resemble those of healthy young adults. Using this model, with alpha-chloralose as the sole anaesthetic, Ross and Cole [14] reported a wide variation in baseline heart rate and arterial pressure and, consequently, the effects of SNP were extremely variable. We found that the addition of phenoperidine ensured that the baseline heart rates and arterial pressures were within the normal range for the conscious animal.

In order to minimize the possible influence of the effects of the first infusion upon the second, we ensured that the degree and duration of hypotension were compatible with full recovery to the baseline haemodynamic state, and that the doses of nitroprusside used were less than toxic, as reflected in acid-base status and blood lactate concentrations remaining normal throughout. Furthermore, the cardiovascular effects of TNP were shown to be almost identical with those of similar infusions given to the same dog 2 h later (fig. 2).

To produce equivalent degrees of hypotension, smaller doses of TNP (and, therefore, nitroprusside ions) were required. Lower HCN concentrations resulted (fig. 4), although neither drug produced potentially toxic HCN concentrations. In addition, TNP produced hypotension by reducing systemic vascular resistance without a significant increase in cardiac output, but with tachycardia which often persisted when the infusion ended.

The demand remains for a short-acting hypotensive drug which may be safely infused to patients without causing a reflex increase in heart rate and cardiac output, and without necessitating recourse to a beta-adrenoceptor blocker. In our opinion, in our animal model, TNP has not been shown to be significantly better then SNP for short term use. It may be more suitable, however, for long-term control of arterial pressure, particularly as the resultant cyanide concentrations would be appreciably lower.

APPENDIX

STANDARD FORMULAE

$$\text{Cardiac index} = \frac{\text{cardiac output}}{\text{body weight}}$$

$$\text{Stroke volume index} = \frac{\text{cardiac index}}{\text{heart rate}}$$

$$\text{Systemic vascular resistance index} = \frac{\text{mean arterial pressure}}{\text{cardiac index}}$$

$$\text{Pulmonary vascular resistance index} = \frac{\text{mean pulmonary arterial pressure}}{\text{cardiac index}}$$

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EFFECT OF THE PREOPERATIVE ADMINISTRATION OF WATER ON GASTRIC VOLUME AND pH

E. M. McGRADY AND A. G. MACDONALD

SUMMARY

Since the preoperative administration of water might promote gastric emptying and dilute the remaining gastric contents, 50 patients were investigated before elective surgery. One group was given water 100 ml 2 h before operation; the other group was fasted as usual. Volume and pH of gastric contents were measured immediately after the induction of anaesthesia. Although the mean gastric residue was less in those patients who were given water, the differences were not statistically significant. There was no difference in gastric pH between the two groups.

One of the anaesthetist's major anxieties at the time of induction of anaesthesia is the risk that the patient may regurgitate, aspirate acid gastric contents and, subsequently, develop the Pulmonary Acid Aspiration Syndrome. To minimize this risk, patients presenting for elective procedures are traditionally fasted for a variable length of time, usually greater than 6 h and often overnight. Despite this precaution, many patients have gastric contents of high volume and acidity on arrival in the anaesthetic room. Hester and Heath [1] demonstrated, in 53% of elective patients, that the pH of the gastric content was less than 2.5. As a figure of 3.0, or even 3.5, is probably more acceptable as the critical pH, it may be that even more patients are at risk [2].

An interesting incidental finding, of a study which compared the oral and i.m. administration of diazepam as a premedicant, was that those patients who were given diazepam by mouth and 50 ml of water to drink showed a significant decrease in both volume and acidity of gastric content [3]. The administration of water may have been entirely beneficial to those patients. In another study, patients given a light breakfast of tea and toast on the morning of operation showed no significant difference in either volume or pH of gastric content when compared with a fasted group [4]. The aspiration of food particles may still be hazardous, even when the pH is above the critical value [5].

A study in children showed that those given orange squash 2 h before the induction of anaesthesia showed a significant increase in volume and acidity of gastric contents [6]. However, these children were given a relatively large volume of fluid—10 ml kg^{-1}, equivalent to 700 ml in a 70-kg adult.

In the light of these studies, it was decided to investigate the effect of administering 100 ml of water to patients 2 h before the induction of anaesthesia. It was postulated that the water, being clear fluid, would leave the stomach rapidly, carrying with it the residual gastric content. In addition, but of less importance, the water might dilute the gastric content, thus increasing the pH. Dilution by a factor of 10 would be necessary to increase the pH value by one unit: for example, 10 ml of residual gastric juice of pH 2.0 would be diluted to approximately 100 ml of pH 3.0.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Fifty gynaecological and general surgical patients presenting for elective surgery were investigated. Patients with a history of any disorder which might impair gastric emptying were excluded from the trial. Informed consent was obtained and patients were randomly al-

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located to one of two groups. Group A were fasted overnight before receiving 100 ml of water approximately 2 h before the induction of anaesthesia. Group B were fasted overnight and received no water. Both groups were given premedication i.m. approximately 1 h before induction of anaesthesia; patients in group A, therefore, received their premedication 1 h after receiving the water. A standard premedication of pethidine and promethazine was administered according to weight. Patients weighing less than 60 kg received pethidine 50 mg and promethazine 25 mg; patients weighing between 60 and 80 kg received pethidine 75 mg and promethazine 37.5 mg; patients weighing more than 80 kg received pethidine 100 mg and promethazine 50 mg.

Anaesthesia was induced with thiopentone and suxamethonium, and a 16-gauge double-lumen orogastric tube was passed before (for ease of insertion) tracheal intubation. With the patient lying supine, the orogastric tube was first aspirated with the tip of the tube 75 cm from the incisor teeth. The tube was then withdrawn gradually, aspiration being performed at 65, 55 and 45 cm. The tube was then re-inserted to 75 cm, the patient was turned to the left lateral position and the aspiration procedure repeated. This procedure was adopted with the aim of ensuring maximal emptying of the stomach. The anaesthetist who performed the aspiration was unaware to which group the patient belonged.

The volume of the gastric aspirate was measured in a graduated measuring cylinder, and pH with a Radiometer pH M 82 electrode. The pH and volume data in the two groups were compared using the Mann–Whitney *U* non-parametric test.

RESULTS

Six patients were excluded from the statistical analysis: one patient's operation was cancelled after he had been given water; another was excluded because he had not received his premedication; in another patient, it was not possible to pass an orogastric tube; three other patients were currently receiving histamine-2 blocking drugs and, although they were included in the trial, it was subsequently decided to withdraw them from the study.

TABLE I. *Details of patients studied. Mean values ± SD*

Group	Age (yr)	Weight (kg)	Period of fast (min)
A (Water) (*n* = 23)	47.6±17	67.6±12.9	131.8±26.5
B (No water) (*n* = 21)	42.8±16	58.1± 8.0	725.3±91.3

TABLE II. *Volume and pH for group A (who received 100 ml of water) and group B (who received no water). Significance of difference between median values*: *P > 0.05

Group A			Group B		
Patient No.	pH	Volume (ml)	Patient No.	pH	Volume (ml)
1	1.37	8	1	1.49	54
2	1.33	35	2	1.23	52
3	1.31	5	3	1.33	18
4	1.22	23.5	4	1.28	15
5	2.24	51.5	5	1.31	43
6	1.19	20	6	no aspirate	0
7	1.27	32	7	1.38	33
8	4.72	6	8	1.67	25
9	1.37	46	9	1.18	15
10	3.08	13	10	3.54	15.5
11	2.43	16.5	11	1.12	15
12	1.09	8	12	1.21	29
13	1.35	28	13	4.0	2
14	6.76	9.5	14	1.29	52
15	7.29	9.0	15	1.39	43
16	1.31	61	16	1.35	43
17	1.28	21.5	17	1.13	15
18	1.46	11	18	1.37	13
19	2.8	12	19	1.38	58
20	7.6	12	20	1.65	16
21	1.34	22	21	1.49	28
22	6.1	4			
23	3.14	50			
Median	1.37	16.5*		1.36	25*
Range	1.09–7.6	4–51.5		1.12–4.0	0–58

The two groups were comparable for age, but the patients in group A had a slight, but significantly, greater mean weight (table I). Weight was not controlled in the randomization process and so this was not an unexpected finding. It was thought reasonable to accept that the difference in weight in the two groups would not interfere with the results.

The mean fasting periods are shown in table I. The patients in group A (given water) had a mean fasting time of approximately 2 h and 10 min, compared with those in group B, who were fasted overnight and who had a mean fasting time of approximately 12 h.

The volume and pH of the gastric content aspirated from the patients in the study varied widely (table II). The median volume in group A was smaller than in group B, although this difference was not statistically significant. The median pH values in the two groups were similar and, although more patients in group A had values greater than 2.5, no significant difference was found between the two groups.

DISCUSSION

The volume and pH of the gastric content aspirated from the patients in this study varied widely. Regardless of whether or not patients received water, the volume of gastric aspirate could be large, small or none at all. Similarly, the pH of the aspirate could be either low or high and appeared to be unrelated to the volume obtained. In other words, the findings in any particular patient were entirely unpredictable, are in agreement with those of Hester and Heath [1], and confirm the concealed danger that volumes of highly acid gastric juice could be present in patients presenting for *elective* surgery.

Although the administration of water 2 h before anaesthesia failed to provide safer conditions at induction, neither did it make conditions more dangerous. The volumes of gastric residue in those patients who received water were no greater than in the control group and, therefore, the ingested water must have left the stomach. This emptying may have taken place very soon after the ingestion of the water, or at any time during the subsequent 2 h, and might have depended on several factors. Cold fluid might stimulate active gastric peristalsis and promote early emptying. The mobility of the patient during the period of 1 h, after ingesting the water and until receiving the premedication, might influence the gravitational emptying of the stomach. The delaying effect of pethidine premedication is well documented, but this would not become effective until absorption and distribution had taken place, perhaps not earlier than 15–20 min after its administration. It is likely, although by no means certain, that the ingested water would have left the stomach earlier than this. We have no evidence that phenothiazine drugs in general, or promethazine in particular, affect gastric emptying.

The safest time for the induction of anaesthesia would be immediately after the emptying of water from the stomach. At this time the original acid gastric juice would have been carried out with the water, and any remaining gastric content would have been dilute and of higher pH. Any further delay beyond this time would allow the secretion of additional fresh peptic juice (perhaps stimulated by the cooling effect of the water). This may be relevant in interpreting the findings of this study.

The main purpose of the study was to produce safer conditions for inducing anaesthesia. However, the regimen of water administration used did not in fact produce safer conditions, because gastric residues were still markedly acid in the majority of patients in both groups. In the group of patients who received water, five of 23 had greater pH values than any of the patients who received no water. These five patients also had relatively small volumes of aspirate and thus represent the "ideal" result. It seems that the controlled administration of water, as conducted in this study, may not be harmful to patients. If the timing of this administration can be gauged correctly, it could be beneficial. Perhaps the 2-h delay before induction of anaesthesia was too long. The results of the study are sufficiently encouraging to justify further investigation.

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PRESSURE REVERSAL OF ANAESTHESIA: A SYNAPTIC MECHANISM

J. J. KENDIG, Y. GROSSMAN AND M. B. MACIVER

SUMMARY

Hyperbaric pressure induces seizures and increases anaesthetic requirements ("pressure reversal of anaesthesia"), but both pressure and anaesthetic agents depress excitatory synaptic transmission. The present study has attempted to resolve this paradox. The interaction between helium pressure to 10.1 MPa and anaesthetic agents (pentobarbitone, halothane, methoxyflurane) was investigated at a crustacean glutaminergic excitatory neuromuscular junction which can be modulated by GABA inhibition. Both pressure and the anaesthetics depressed the singly evoked excitatory junctional potential (EJP). During repetitive stimulation, both pressure and pentobarbitone antagonized their own depressant effects by enhancing tetanic potentiation. The additive enhancement at 10.1 MPa was sufficient to increase the pentobarbitone-depressed response above the corresponding normobaric level. No significant antagonism between pressure and any of the anaesthetics was observed on the properties of EJP amplitude and time course, facilitation, potentiation or inhibition. Additivity rather than antagonism is the basis for pressure reversal of anaesthetic depression at this model synapse. The functional antagonism is therefore indirect, and probably involves multiple sites of action for both pressure and anaesthetics.

Hyperbaric pressure in the range of several MPa (0.1 MPa = approximately 1 atmosphere) causes anaesthetized animals to resume behaviour characteristic of the awake state. This phenomenon of pressure "reversal" of anaesthesia has been used to test theories of the mechanism of anaesthesia, under the assumption that pressure–anaesthetic antagonism represents a physical reversal of anaesthetic action [1–6]. Unitary hypotheses of anaesthesia postulate a common single action, such as a volume increase or a change in membrane fluidity, for all anaesthetic agents [7–10]. A multisite hypothesis of anaesthetic action has also been proposed, based on evidence that the curve describing the pressure effect on the anaesthetic ED_{50} differs between agents [11–13].

Attempts to explain pressure reversal of anaesthesia at the cellular level have encountered major difficulties. Potentially excitatory effects of pressure in axonal membrane, for example [14, 15], are probably not of sufficient magnitude or universality [16] to overcome the profound depression of excitatory synaptic transmission observed at high pressure in all synapses which have been studied to date [17–21]. Pressure adds to the depressant effect of anaesthetics [18, 22, 23]. To account for pressure reversal of anaesthesia, pressure must exert some effect that directly or indirectly antagonizes this depression to an extent that brings the level of excitation above the anaesthetic-depressed level at 0.1 MPa.

In a separate study [24], we reported that pressure enhances the synaptic integrative properties of facilitation and tetanic potentiation. The effect increases synaptic efficacy and antagonizes the depressant effect of pressure on singly evoked responses. Enhancement of synaptic potentiation is therefore a possible mechanism of pressure reversal of anaesthesia or of the seizures associated with high pressure.

The present study was designed with two

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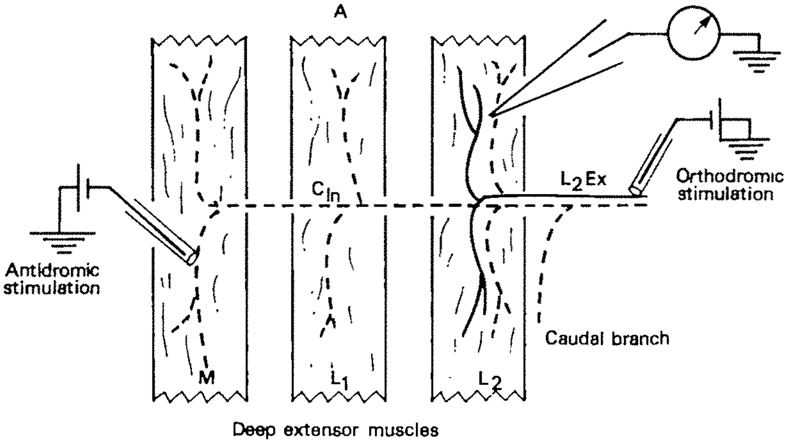

FIG. 1. Arrangement for stimulating motor neurones and recording from individual muscle cells. The deep abdominal extensor muscles of lobster were excised and the motor nerve dissected free as described in the text. A = cephalad direction. M, L_1 and L_2 are the three divisions of this muscle group. A single excitor motor neurone (L_2Ex) innervates only the lateral division (L_2) of the muscle. A single inhibitory motor neurone (C_{In}) also innervates the muscle; it can be stimulated either independently (antidromic stimulation) or concurrently with L_2Ex. A recording electrode is placed in one of the muscle cells of the L_2 division.

purposes: to test if the synaptic depressant effect of an anaesthetic agent can be reversed by enhanced potentiation; and to examine if such a reversal represents a direct or an indirect antagonism. Experiments were carried out in a crustacean muscle innervated by identifiable single excitatory and inhibitory motor neurones. Most of the experiments examined the interaction between pressure and a barbiturate general anaesthetic, pentobarbitone; for comparison, some experiments used the volatile anaesthetic agents halothane and methoxyflurane. The results have been reported in summary at a meeting [25].

MATERIALS AND METHODS

The deep extensor muscles of lobster (*Panulirus interruptus* or *Homarus americanus*) were excised and mounted to permit independent stimulation of individual excitatory and inhibitory motor neurones. The muscle was mounted in a bath constantly perfused with oxygenated Ringer's solution of the appropriate composition for each species (fig. 1). For *Homarus*, this was artificial sea water of composition (mmol litre^{-1}): NaCl 460; KCl 10; $CaCl_2$ 10; $MgCl_2$ 20. For *Panulirus*, the composition (mmol litre^{-1}) was: NaCl 520; KCl 12; $GaCl_2$ 12; $MgCl_2$ 10. Both solutions were buffered with HEPES 5 mmol litre^{-1}, and pH was adjusted to 7.4. In experiments in which inhibition was examined, $CaCl_2$ concentration was increased 20% and $MgCl_2$ correspondingly reduced; glucose 5 mmol litre^{-1} was added. Temperature was monitored by a thermistor in the bath and maintained at approximately 19 °C. Muscle cells were impaled by a microelectrode filled with potassium acetate 3 mol litre^{-1}, resistance 10–30 MΩ.

Excitatory junctional potentials (EJP) were amplified, digitized (Scientific Solutions Labmaster) and stored on disc for later analysis by microcomputer-based software (pClamp, Axon Instruments). Singly evoked EJP analysed for amplitude and temporal properties are averages of 15 individual responses, as are paired responses analysed for facilitation. Responses to trains of stimuli are not averaged. Illustrations of EJP were generated from the digitized records and plotted on an H-P 7470A plotter. Membrane resistance was measured and current–voltage curves obtained by injecting current through the recording microelectrode and monitoring the resultant changes in voltage.

After control records were obtained, the preparation was perfused with solution containing one of the three anaesthetic agents. Pentobarbitone was dissolved in solution to achieve a concentration of $1–5 \times 10^{-4}$ mol litre^{-1}, a range of concentrations which brackets the anaesthetic dose for this agent. Methoxyflurane and halothane were

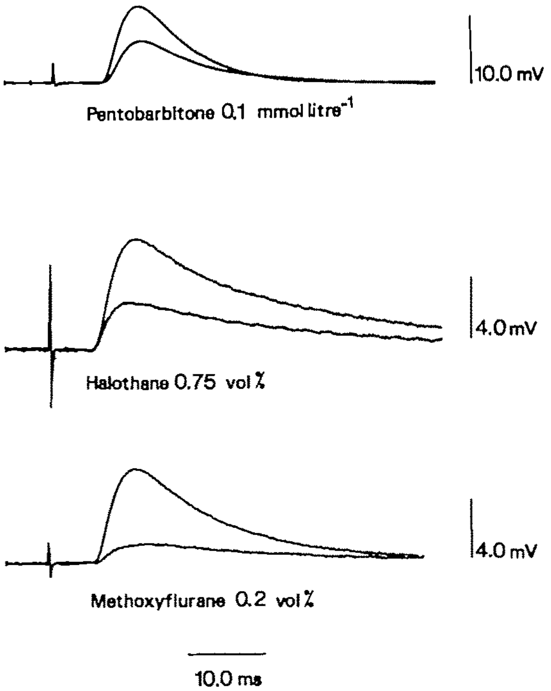

FIG. 2. Depression of excitatory junctional potential (EJP) amplitude by pentobarbitone, halothane and methoxyflurane at the concentrations indicated. Each trace shows control and anaesthetic-depressed responses superimposed.

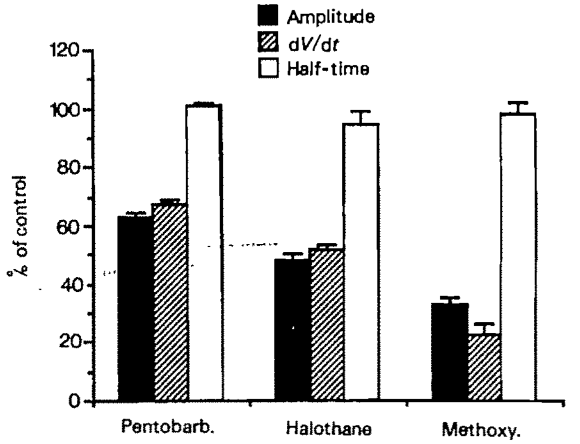

FIG. 3. Anaesthetic effects on EJP amplitude and kinetics. Pentobarbitone 1–2 × 10^{-4} mol $litre^{-1}$, 0.5–1 % (v/v) halothane and 0.1 % (v/v) methoxyflurane significantly depressed the amplitude and rate of rise (dV/dt) of the excitatory junctional potential; none of the agents significantly altered the half-time of the EJP decay.

mixed with oxygen by calibrated vaporizers in concentrations of 0.1–0.4 % v/v (methoxyflurane) and 0.5–3.0 % v/v (halothane); these concentrations range from slightly below to well above the clinical anaesthetic range. The perfusing solution was equilibrated with the gas mixture by bubbling for at least 30 min. Records of the anaesthetic effect were made 20–30 min after perfusion had begun with a given concentration of the agent, when the effects were at a steady state. Reversibility was assessed by washing with drug-free solution. Twelve experiments at normobaric pressure were undertaken with pentobarbitone, five with halothane, and five with methoxyflurane.

Pentobarbitone was the agent used in all pressure studies. For pressure experiments, the preparation was mounted for intracellular recording as described above, placed in a pressure chamber, and perfused continuously with oxygenated Ringer's solution. Control recordings were made after the chamber was sealed. Pressure was applied by admitting helium from a high-pressure cylinder. Details of the pressure chamber, compression regimens and temperature control were as described previously [26]. Measurements at pressure were made 20 min or more after the compression step. Sixteen experiments were completed in which both pressure and pentobarbitone were applied to the same preparation. In five of these, control measurements were made, the preparation was compressed to 10.1 MPa, the effect of pressure determined, and pentobarbitone applied at pressure. In the remainder, the effects of pentobarbitone at 0.1 MPa were determined and the preparation then compressed to 10.1 MPa. Additional experiments were undertaken with pressure alone. Comparisons were made between the effects of pentobarbitone at normal pressure and at 10.1 MPa, and between the effects of pressure with and without pentobarbitone. Data were analysed by ANOVA to reveal anaesthetic interaction with pressure effects and *vice versa*; in addition *t* tests for paired values were carried out in those cases in which the data were obtained from the same preparation.

RESULTS

Sensitivity of the junction to anaesthetics

Preliminary experiments were carried out to confirm the sensitivity of the glutaminergic excitatory junction to clinically relevant anaesthetic concentrations. Examples of the depressant effects of pentobarbitone, halothane and methoxyflurane

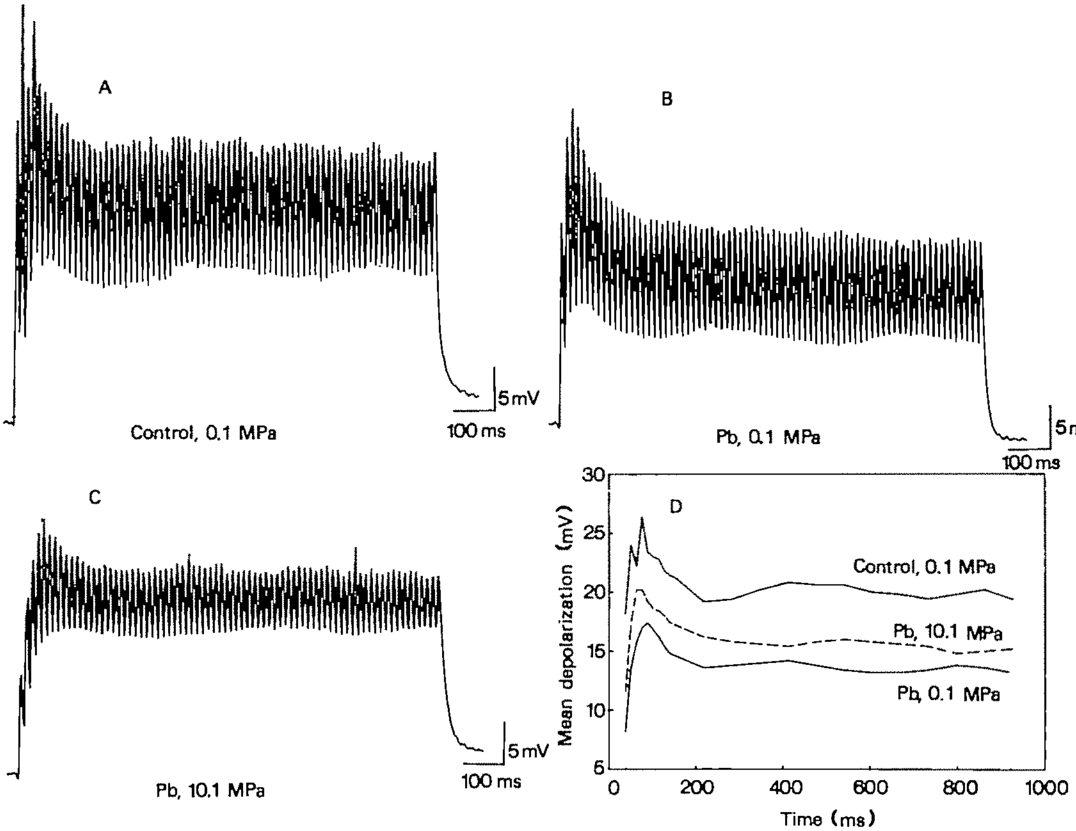

FIG. 4. Enhancement of potentiation can reverse the depressant effects of pentobarbitone and pressure. Records A, B and C are the responses to the fifth of a series of five trains of stimuli at 75 Hz, train repetition rate 0.5 Hz. The potentiated response (A) is reduced by pentobarbitone (Pb)10^{-4} mol litre^{-1} (B); application of 10.1 MPa pressure increases the response amplitude (C). Graph D shows the mean depolarization during the train—one measure of the excitatory input to the junction. Pressure increased both peak and mean depolarization above the anaesthetic-depressed level measured at normobaric pressure.

are shown in figure 2. Synaptic dose–response curves were not constructed; however, the lowest concentration of pentobarbitone, 10^{-4} mol litre^{-1}, depressed EJP amplitude by at least 20 % and the highest, 5×10^{-4} mol litre^{-1}, by at least 75 %. Halothane 0.5–1 % depressed responses by at least 20 %; 1.5 % by at least 75 %. Methoxyflurane 0.1 % depressed responses by at least 20 %; concentrations greater than 0.2 % nearly abolished the response. The effects of the anaesthetics on amplitude and time course of the excitatory junctional potential (EJP) are shown quantitatively in figure 3. The depression of the EJP amplitude and rate of increase (dV/dt) were significant for all three agents ($P < 0.05$). The decay rate of the EJP was of particular interest as a potential measure of pressure–anaesthetic antagonism, since pressure prolongs the declining phase of the EJP [24]. Although pentobarbitone appeared to increase the rate of decay in some preparations, the effect was not significant. There were no apparent effects of halothane or methoxyflurane on decay half-time (fig. 3). None of the anaesthetics significantly or consistently altered muscle resting potential or resistance as measured by the current/voltage relationship.

In each preparation, a single anaesthetic concentration was chosen at which other synaptic properties were measured, using the criterion of a mid-range depression of singly evoked EJP amplitude. Amplitudes of the anaesthetic-depressed EJP at concentrations at which the properties of facilitation and potentiation were measured were 47.9 % ± 11 (SD) of control (drug-free) values for

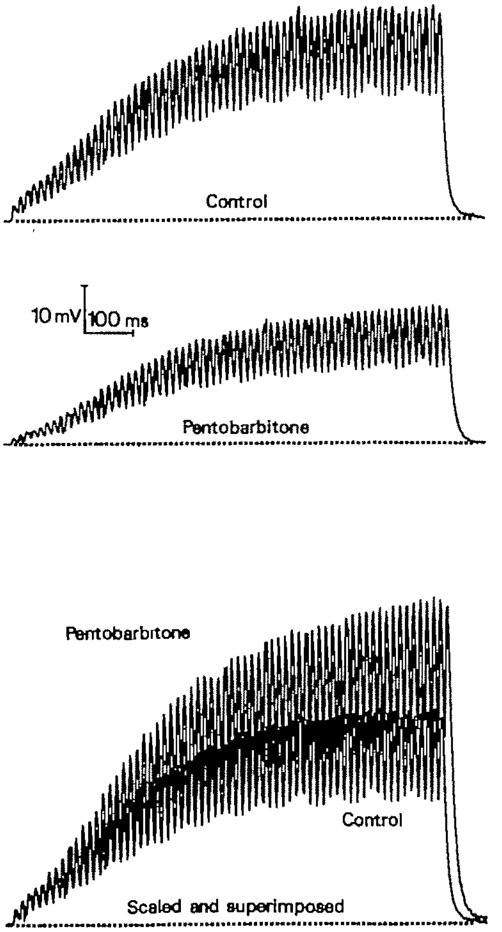

FIG. 5. Effect of pentobarbitone 10^{-4} mol litre^{-1} on tetanic potentiation at normal pressure. Control (top) and pentobarbitone-depressed (middle) responses to a train of stimuli at ~70 Hz, plotted to the same scale. Below, the pentobarbitone-depressed response scaled upward so that the first EJP of the train matches the control amplitude, and superimposed on the latter. Potentiation increased markedly in the presence of pentobarbitone.

halothane, 33.2% ± 5 for methoxyflurane, and 62.7% ± 18 for pentobarbitone.

Activity-dependent pressure reversal of anaesthetic synaptic depression

We used repetitive trains of stimuli to test if pressure enhancement of tetanic potentiation antagonized pentobarbitone-induced synaptic depression. The pattern consisted of a train 0.9 s long, stimulus frequency within the train 60–90 Hz, repeated five times at a train repetition rate of 0.5 Hz. Repetitive stimulation at 10.1 MPa increased the pentobarbitone-depressed response above the comparable normobaric level (fig. 4). The result was a partial reversal of pentobarbitone-induced synaptic depression. Peak and mean levels of depolarization were greater at 10.1 MPa than at normal pressure in the presence of pentobarbitone. This is the first time pressure reversal of anaesthetic effects has been demonstrated at a synapse.

Is the reversal a pressure–anaesthetic antagonism?

Pressure reversal of anaesthetic effects on synaptic transmission through enhancement of tetanic potentiation might represent direct antagonism if anaesthetic agents depressed synaptic potentiation. Our results did not support this possibility. Pentobarbitone enhanced the build up of tetanic potentiation at normobaric pressure (fig. 5), thus antagonizing its own depressant effects in an activity-dependent fashion. Potentiation was quantified by measuring the amplitude from baseline of the last response in a 0.9-s train relative to the first; stimulus frequency within the train was 40–90 Hz. Pentobarbitone was associated with a mean increase in potentiation of approximately 25% in eight experiments; this effect was significant ($P < 0.01$).

A series of experiments was carried out to test if volatile agents behaved differently from barbiturates in this respect. Neither halothane nor methoxyflurane decreased potentiation. Thus for the volatile agents, in addition to pentobarbitone, there was no evidence for pressure–anaesthetic antagonism.

Paired-pulse facilitation

Potentiation as measured in this study included summation, the short-term process of facilitation, and one or more longer term processes. Our previous studies [24] showed that pressure significantly enhanced the facilitation evoked by paired stimuli to the excitor motor neurone. Experiments were carried out to test if anaesthetics antagonized the effect of pressure on facilitation. The effect of pressure on paired-pulse facilitation was maximal at an interpulse interval of 10 ms; accordingly, this interval was chosen to examine the effects of anaesthetics. At this short interval a portion of the enhancement of the response to the second stimulus resulted from summation. Data were analysed with this component included (facilitation + summation) and with the summation component subtracted digit-

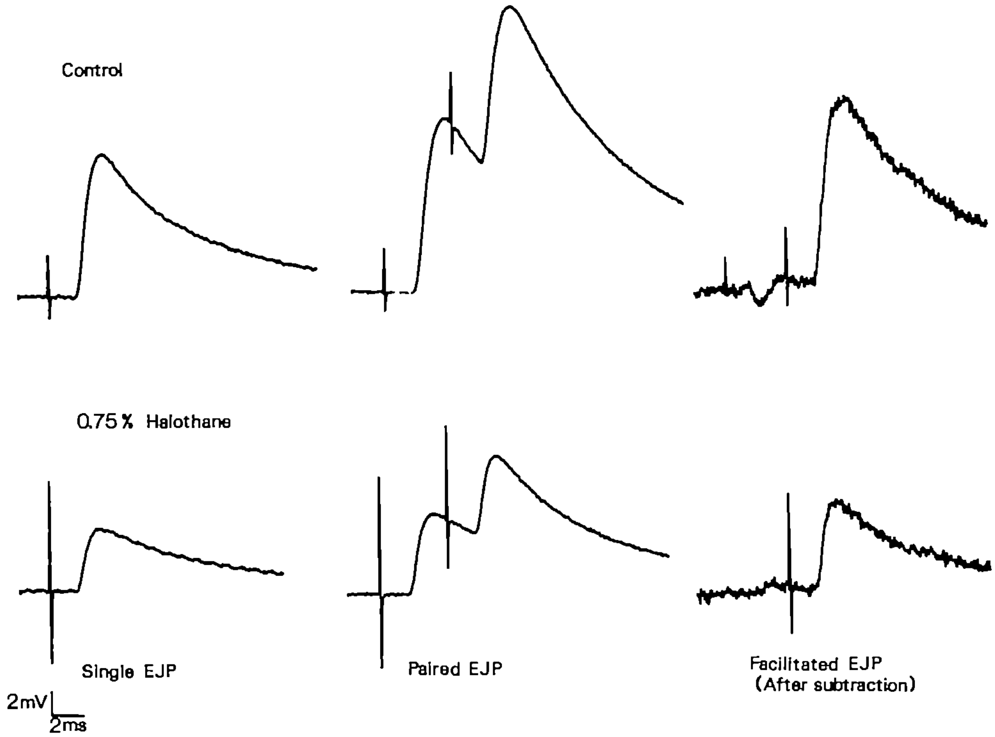

FIG. 6. Paired pulse facilitation: method of measurement and effect of halothane. Upper row, control; lower row, halothane-depressed EJP. Left column, a single stimulus evoked a single EJP; centre, the response to two closely spaced stimuli was a pair of EJP; the amplitude of the second (P_2), measured from the baseline, was increased by summation with the first (P_1) and by synaptic facilitation. Single and paired responses were averages of 15. Right column shows the method of correcting for summation. A single EJP from the records was selected to match the amplitude of the first of the pair, and subtracted digitally from the pair record. The difference was the second response with summation removed, showing an enhanced amplitude produced by facilitation alone. Halothane did not depress facilitation, measured as the amplitude of the second response referred to the first.

ally as shown in figure 6, to give a measure of facilitation alone.

The effects of halothane, methoxyflurane and pentobarbitone on facilitation + summation and on facilitation alone are shown graphically in figure 7. No agent depressed each measure of paired-pulse facilitation. For pentobarbitone and halothane, but not methoxyflurane, there was a consistent enhancement of the values for facilitation, but this was too small to be significant.

The role of inhibition

Barbiturate enhancement of GABA-mediated inhibition has often been observed. In this crustacean preparation, the single GABA-ergic inhibitory motor neurone can exert marked depressant effects on the excitatory response. Since the reversal potential for the inhibitory junctional potential (IJP) is close to the normal resting potential, normally the IJP is small or undetectable. Inhibition is therefore monitored most easily by effects on the EJP. An example of inhibition is shown in figure 8. At normobaric pressure pentobarbitone did not significantly affect inhibition in this preparation, measured as a decrease in EJP amplitude or an increase in EJP rate of decay. Pressure depressed inhibition of the EJP to the same extent as pressure depressed the EJP itself [24]. Pentobarbitone did not prevent or reverse the non-selective decrease in inhibition observed on compression to 10.1 MPa (fig. 8).

When the inhibitor was stimulated concurrently with the excitor during a train, the result was inhibition of all the EJP in the train. Because the inhibitory junction also displayed potentiation, the developing inhibition limited the extent of potentiation shown by the excitor. Pentobarbitone did not significantly modify inhibition during a

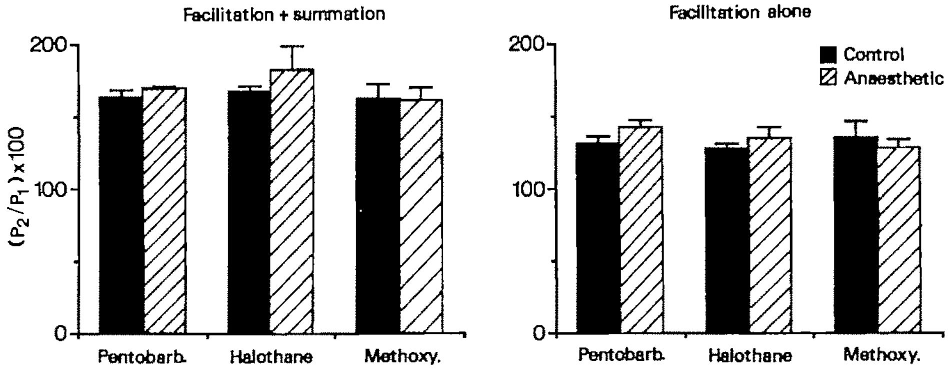

FIG. 7. The effects of pentobarbitone 1–2 × 10^{-4} mol $litre^{-1}$, 0.5–1 % (v/v) halothane and 0.1 % (v/v) methoxyflurane at normal pressure on facilitation with summation and facilitation alone as obtained by the methods shown in figure 6. Vertical axis is the amplitude of the second (P_2) of a pair of responses 10 ms apart, divided by the amplitude of the first (P_1), and expressed as a percentage. None of the agents decreased facilitation at concentrations which significantly depressed EJP amplitude.

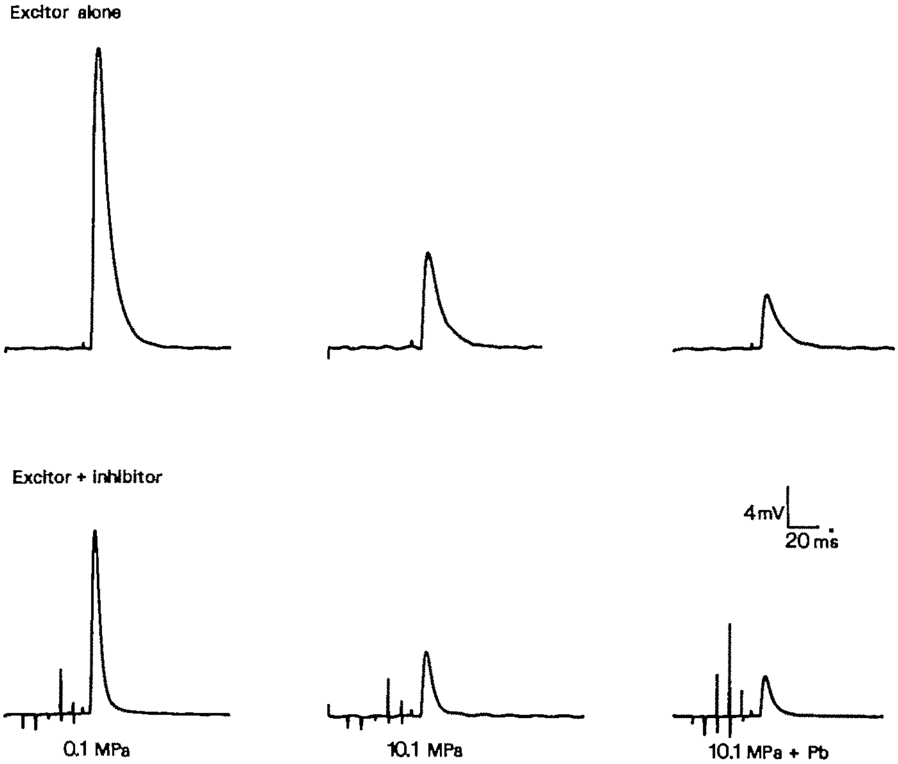

FIG. 8. Pressure and barbiturate effects on excitatory and inhibitory junctional transmission. Top: the L_1Ex stimulated alone to elicit an EJP (excitor alone). Bottom: the EJP inhibited by a train of five stimuli to the inhibitor preceding the stimulus to the excitor (excitor + inhibitor). Left: controls at 0.1 MPa. Middle: compression to 10.1 MPa depressed both EJP and the amount of inhibition to a comparable extent. Right: pentobarbitone 10^{-4} mol $litre^{-1}$ applied at 10.1 MPa augmented the depressant effect of pressure on the EJP and did not change the extent of inhibition.

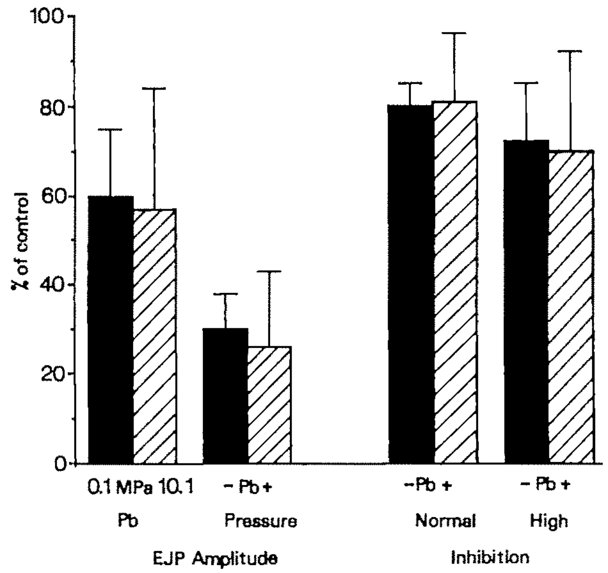

FIG. 9. Depression of EJP amplitude by pentobarbitone was the same at normal and hyperbaric pressure. Depression by pressure was the same with and without pentobarbitone present. The same was true for inhibition. Vertical axis: EJP amplitude or inhibition as percent of the appropriate control. Left pair of columns: Pentobarbitone (Pb) depressed EJP amplitude to the same extent applied at both 0.1 (solid) or 10.1 (shaded) MPa. Second pair: pressure depressed EJP amplitude to the same extent in drug-free (−, solid) or Pb (+, shaded) solutions. Inhibition was the same at normal and high (10.1 MPa) presssure in drug-free (−, solid) or Pb-containing (+, shaded) solutions. Pentobarbitone concentrations: 1–5 × 10^{-4} mol litre^{-1}.

train of stimuli, either at normal or at hyperbaric pressure (fig. 9). In this preparation, enhancement of inhibition by the anaesthetic did not contribute to overall depression of excitatory transmission. Selective depression of inhibitory transmission by pressure did not contribute to reversal of the anaesthetic effect.

True antagonism?

There appears to be no evidence that pressure and anaesthetics acted antagonistically at this synapse. Both depressed the singly evoked EJP and both enhanced potentiation. Pentobarbitone effects on inhibition did not contribute to anaesthetic depression of the EJP; pressure effects on inhibition did not contribute to activity-dependent pressure reversal of anaesthetic depression. It remains to ask if any "true" antagonism between anaesthetics and pressure exists which is only revealed when both are applied together. Are the effects of pressure different in the presence of the anaesthetic, and *vice versa*? This did not appear to be the case. The pressure at which pentobarbitone was applied did not modify significantly the depressant effect of pentobarbitone on the EJP, and the presence of pentobarbitone did not significantly change the depressant effect of pressure. There was also no interaction on inhibition. The results of both interactions are presented graphically in figure 9. With respect to EJP amplitude and inhibition, therefore, there was no obvious "true" pressure–anaesthetic antagonism that appeared only when the two interventions were applied together. The effects of pressure on facilitation were also not modified by the presence of pentobarbitone.

DISCUSSION

Fundamental effects of the anaesthetics

All the agents significantly depressed the amplitude and rate of rise of the singly evoked EJP at clinically relevant anaesthetic concentrations. Anaesthetic partial pressures (minimal alveolar concentrations, MAC) in man are 0.75–0.77% halothane and 0.16% methoxyflurane. Anaesthetic blood:water values for pentobarbitone are reported in the range 1–6 × 10^{-4} mol litre^{-1} [27, 28]. At this glutaminergic "synapse" in crustacea, therefore, there was a significant depressant effect at anaesthetic concentrations, to an extent similar to that observed at many other excitatory synapses. However, other reports have suggested that crustacean neuromuscular junctions are less sensitive to the effects of some general anaesthetics than are other synaptic preparations [29].

We were particularly interested in the decay phase of the EJP as a possible reflection of direct pressure–anaesthetic antagonism. Pressure slows the decay rate of synaptic currents [21] and potentials [24]. None of the anaesthetics significantly changed EJP decay rate in this study. A decrease in decay time constant for postsynaptic currents has been reported at the vertebrate neuromuscular junction for a variety of anaesthetics [30]. Halothane and pentobarbitone have been reported to increase the rate of decay of currents in a crustacean neuromuscular junction, but only at concentrations above the anaesthetic range for man [29]. The crustacean muscle cell is large, with a low resistance cell membrane. It is possible that there is a basic effect of anaesthetics on EJP current decay time constant which is too small to affect the voltage measurements to which the present study was restricted.

Membrane resistance and resting potential did not change significantly or consistently in the present study. Others have reported anaesthetic-related hyperpolarization related to an increase in conductance in vertebrate CNS neurones [31-33]. The latter have many membrane ion channels which have not been documented as yet in crustacean muscle cells. However, the GABA-activated chloride conductance which has been implicated in some studies as related to the hyperpolarization is present at the inhibitory neuromuscular junction in these cells. Small changes in membrane resting potential, resistance, or both, are not excluded by the results of this study.

Pentobarbitone auto-antagonism: implications for anaesthesia

Pentobarbitone increased tetanic potentiation during a train of stimuli. This is a novel and unexpected finding, although there is a report of possible pentobarbitone-related increases in potentiation in mammalian cortex [34]. The result of this property is that the agent partially antagonizes its own depressant effects on synaptic transmission in the course of the bursts of repetitive activity characteristic of many synapses. Thus, the potency of at least this barbiturate anaesthetic is dependent in part on the normal pattern of activity at a given synapse and the integrative properties of that synapse.

Our results do not permit much speculation on the mechanism of this anaesthetic effect; however, at least one possibility can be excluded. The increase in potentiation seen with pentobarbitone cannot result from a direct effect on presynaptic voltage-dependent sodium channels. Barbiturates, in common with local anaesthetics, block sodium channels in a frequency-dependent manner [35]. Repetitive activity enhances the block, an effect which has been postulated to account for the frequency-dependent block of transmission at the neuromuscular junction observed with the related anticonvulsant, phenytoin [36]. On this basis, action potential amplitude in the presynaptic terminal would tend to be reduced progressively during a train of stimuli. The frequency-dependent effects of barbiturates on the sodium channel would thus act in opposition to the enhancement of potentiation which was actually observed.

Relationship of the findings to the mechanism of pressure reversal

Pressure can "reserve" the depressant effect of pentobarbitone at a neuromuscular junction exposed to repetitive activation. The motivation for this study was our previously reported finding that pressure had some potentially excitatory effects at this junction, prolonging the decay of the EJP, increasing paired-pulse facilitation, and increasing potentiation during a train of responses [24]. In no case did any of the anaesthetics act in a direction opposite to pressure with respect to these three variables, with the possible exception of EJP decay rate, as noted above. Anaesthetics exerted no significant depressant effects on paired-pulse facilitation and one, pentobarbitone, acted in the same direction as pressure on potentiation. The mechanism for pressure reversal of the anaesthetic effect at this synapse is therefore an additive interaction rather than an antagonistic one.

There were no significant interactions between pressure and pentobarbitone with respect to effects on EJP amplitude, inhibition or facilitation. The present data thus provide no basis for "true" antagonism between pressure and anaesthetics of the antagonist–agonist type. As with previous studies, the depressant effects of pressure and anaesthetics on synaptic transmission as measured by singly evoked EJP amplitudes are additive [18, 23]. No studies on neuronal systems have provided evidence for a "true" antagonism not based on opposing independent actions. However, it is conceptually possible, and has been shown in a bilayer model [37].

Potentiation as a mechanism for pressure reversal of anaesthesia

Both pentobarbitone and pressure enhance potentiation, and each antagonizes its own synaptic depressant effect through this mechanism. The frequency-dependent effects of pressure were shown in an early study [20]. Pentobarbitone has been reported to increase potentiation in mammalian cortex [34]. As we have measured potentiation in this study, it includes components of the shorter-term process of facilitation, one or more longer-term processes termed potentiation, and summation.

Summation is a postsynaptic phenomenon, while facilitation and potentiation are predominantly presynaptic. We have shown that pressure enhances facilitation, which is evidence for a presynaptic site of action [24]. The depressant effect of pressure on synaptic transmission results predominantly from depression of transmitter release [21, 38] by an unknown mechanism. Anaesthetics also depress transmitter release [39, 40] by a mechanism which may involve depression of calcium influx [41, 42]. Agents which depress transmitter release, particularly those which do so by blocking or reducing calcium entry, enhance facilitation; in fact, enhancement of facilitation is taken as evidence for a presynaptic site of action [43]. The evidence available thus strongly suggests that both pressure and pentobarbitone enhance potentiation because they both inhibit initial transmitter release. It remains to be determined if they both do so by acting in part on the same process, for example to decrease initial calcium entry.

The increase in potentiation at 10.1 MPa was sufficient to overcome partially the depressant effect of the barbiturate. If this is an important component of pressure reversal of anaesthesia, pressure reversal of anaesthesia does not result from direct antagonism between pressure and anaesthetic actions. The evidence that both pressure and anaesthetic agents act in the same direction on presynaptic processes is presented above. There is evidence that depression of the postsynaptic response accounts for much of the anaesthetic depression of excitatory synaptic transmission [30, 44]. If relief of the depression is a result of actions on presynaptic processes, pressure–anaesthetic antagonism is indirect, at least in large part.

Network properties and the role of inhibition

Pressure depresses GABA-mediated inhibition in this preparation to the same extent as excitation, probably by the same non-selective mechanism of depression of transmitter release [24]. Pressure depression of inhibition does not contribute to an overall increase in excitation, probably because this inhibitory neuromuscular junction also displays prominent facilitation which is enhanced by pressure. In this preparation also, we did not observe pentobarbitone enhancement of inhibition such as has been reported at mammalian synapses [45]. On the other hand, in the mammalian CNS, inhibitory synaptic transmission may play a role in anaesthesia and pressure reversal. There is evidence that, in the hippocampus, inhibition is mediated by tonically active decrementing, rather than facilitating, synapses [46]. The non-selective depressant effect of pressure on inhibition, therefore, might not be counteracted by enhancement of potentiation during repetitive activity. In addition, it has been suggested that glycine rather than GABA is the inhibitory transmitter implicated in pressure-induced seizures [47]. Whether or not inhibition is enhanced by anaesthetics, the combination of facilitating excitatory synapses and non-facilitating inhibitory synapses characterizes a network of which the level of excitation might be readily increased by pressure, by the mechanism we propose. Pressure reversal, rather than defining the molecular site of anaesthetic action, may thus constrain the network integrative properties of the CNS site of anaesthesia.

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OBSERVATIONS CONCERNING THE NATURE OF SITES OF ANAESTHETIC ACTION IN *GAMMARUS*

J. R. ELLIOTT AND A. A. McELWEE

SUMMARY

We report the effects of n-alkanols (n-butanol to n-octanol), methyl carboxylic esters (methyl propionate to methyl octanoate) and n-alkyl ketones (2-pentanone to 2-nonanone) on a fast reflex escape response to a mechanical stimulus in Gammarus. *ED_{50} concentrations and the relationships between ln ED_{50} and chain length are given for each compound and series. For the n-alkanols, this relationship is well fit by a straight line ($r^2 = 1.000$), with no evidence for a plateau between hexanol and heptanol. The standard free energy of transfer of a methylene group from water to a site of action in* Gammarus *is given for each series. The value for the esters is significantly smaller than that for the n-alkanols and ketones. These free energies are compared with those from other model systems, with the conclusion that further investigation of the differences between n-alkanols and esters will increase our understanding of the physicochemical nature of the site(s) of action of general anaesthetics.*

Studies of the mechanism of general anaesthesia depend, in the main, on the use of models. One of the earliest model systems, a beaker of olive oil, was developed from the work of H. H. Meyer [1] and of Overton [2] at the turn of the century. They showed that the anaesthetic potency of a wide range of anaesthetic agents was directly related to the partition coefficient between water and a hydrophobic medium such as olive oil. This result has been interpreted as indicating that the site (or sites) of action of anaesthetics is hydrophobic, and an extreme interpretation would be that the site is actually composed of lipid molecules. Knowledge of the physicochemical nature of the primary anaesthetic site would be very useful, as it could lead to the production of more precisely targeted anaesthetic agents with fewer side effects. Unfortunately, the Meyer–Overton correlation does not get us very far in defining the nature of the site, simply because there are so many possible hydrophobic sites and models.

Studies of the action of homologous series of compounds (where successive members differ only in the number of methylene groups in the molecule—for example n-hexanol with five and n-heptanol with six) have, however, provided a further criterion for any model site—a "cut-off" in activity as the series is ascended. Thus for the n-alkanol homologous series, n-butanol is more potent than n-propanol, as predicted by the Meyer–Overton correlation, but this increase in potency is not carried on throughout the series, since n-tetradecanol is inactive [3, 4]. This cut-off in activity of large, but very hydrophobic, molecules is consistent with a site of restricted geometry, but not with the "olive oil" model.

It has been suggested [5] that the data on general anaesthetic potency for n-alkanols contains diagnostic information about the nature of the site well before the cut-off point. Franks and Lieb [5] have reported the effects of n-alkanols on the water-soluble protein firefly luciferase (used as a pure protein model for the anaesthetic site). Broadly speaking, the potency data obey the Meyer–Overton correlation up to a cut-off point at about hexadecanol. However, the luciferase data for n-hexanol and n-heptanol deviate substantially from the correlation, the two alkanols being approximately equipotent rather than showing the predicted increase in potency by a factor of approximately four on going from n-hexanol to n-heptanol. The worth of luciferase, or any other isolated system, as a model for a general anaesthetic site can only be judged by comparison with

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data from a whole animal. The luciferase study included every alkanol from methanol to n-hexadecanol; the difficulty in assessing the relevance of the "anomalous" hexanol and heptanol result to general anaesthesia lies in finding a study on whole animals which covers every alkanol in the range of interest, say from butanol to octanol. The work of Meyer and Hemmi [3] omitted a crucial alkanol, n-hexanol. Franks and Lieb [5] tried to overcome this omission by joining the data of Meyer and Hemmi [3] to those of Vernon [6] and comparing luciferase data with these hybrid anaesthesia data (see figure 3 of reference [5]). We felt that a single study of the effects of n-alkanols on the activity of a whole animal would provide a more satisfactory comparison. Thus the major part of this paper is a report of the relative effectiveness of n-butanol, n-pentanol, n-hexanol, n-heptanol and n-octanol in abolishing a reflex response in *Gammarus*, the freshwater shrimp. (The usefulness of a freshwater shrimp as a model for anaesthesia in man is a question we leave open for the reader...)

The second part of this work is a comparison of the effects of different homologous series on *Gammarus*. The Meyer–Overton model predicts that the change in potency observed on ascending a homologous series will be roughly constant for all series, since that is the behaviour observed in model solvents. However, such is not the case in an isolated nerve. Elliott, Murrell and Haydon [7] have studied the local anaesthetic action (reduction in peak sodium current in the squid giant axon) of members of the methyl carboxylic ester series and have compared the effects of esters with those of the n-alkanols [8]. As the series was ascended, the potency of the alkanols increased by a factor of 3.7 for each additional methylene group; for the esters, the increase was only a factor of 2.9. One interpretation is that alkanols and esters act at the same site in the squid axon membrane, but that a single site somehow discriminates between the two classes of chemical. Another is that there are subtly different primary sites of action for esters and alkanols. In this paper, we extend the comparison between esters and alkanols by reporting an investigation of general anaesthetic action and we have also studied a related series, the n-alkyl ketones, to see if they act like esters or like alkanols.

A preliminary report of part of this work has been communicated to the Physiological Society [9].

MATERIALS AND METHODS

The end-point used to determine "anaesthesia" in *Gammarus* was the loss of a very fast, co-ordinated escape response to a sharply administered mechanical stimulus on either lateral surface. The response was found to be very reproducible and abolition was readily reversible. It did, however, have the disadvantage that each animal must be tested individually by hand.

Fifty to 100 *Gammarus* were maintained in a colony and animals were taken at random for each experiment. They were tested for responsiveness to the stimulus before administration of any test compound. For each concentration of test substance, six *Gammarus* were placed in a beaker containing 400 ml to 2 litre of solution and their response observed until a steady state was obtained. A control group of six animals was monitored simultaneously for the majority of the alkanol experiments and then for each new batch of animals or initial use of a new stock solution. Controls showed no loss of activity. When a steady state was reached the test animals were transferred to a beaker of control solution and their responses observed to recovery. In a few experiments (< 10) an animal died, otherwise recovery was total. Fully recovered animals were returned to the colony and could, therefore, have been used in the next experiment, but no animal would have been used more than twice in one day. The time taken to reach a steady state depended on the type and concentration of test substance, and varied between 4 and 40 min. Recovery was usually complete within 10 min. Some "blind" experiments were performed, in which the experimenter did not know the type or concentration of test solution, with no difference in result.

The possibility of significant depletion of the test substance in the aqueous phase by adsorption to the animals was considered. Data concerning the partitioning of n-alkanols between water and lipid membrane phases [4] were used to calculate the volume of test solution required for negligible depletion, on the worst case assumption that the total *Gammarus* volume was lipid. Thus while 400 ml was considered ample for most test compounds, this was increased to 1.5 or 2 litre for the highest members of each homologous series.

Some experiments were carried out using n-propanol, at concentrations between 10 and 40 mmol litre^{-1}. These were not continued, as a significant proportion of the animals died (and turned orange). Experiments using sucrose solutions of the same molarity showed that this was not simply an osmotic effect.

All inorganic chemicals were Analar grade from B.D.H. Ltd (Poole, Dorset) and all organic test compounds were purum or puriss grade from Sigma Chemical Co. (Poole, Dorset) or Fluorochem Ltd (Glossop, Derbyshire). Solutions were prepared gravimetrically. Ester solutions were used on the day of preparation, as significant hydrolysis to the parent carboxylic acid occurs over a period of days. Experiments were carried out at room temperature (approx. 20 °C).

Gammarus were obtained from Blades Biological (Edenbridge, Kent) and were maintained in aerated "artificial canal water", which was also used to make up the test solutions. This contained (mmol litre^{-1}); NaCl 0.5; $KHCO_3$ 0.25; $CaSO_4$ 0.5; $MgCl_2$ 0.25; pH approx. 7.5. We are indebted to Dr P. Taylor for suggesting this solution to us, as the animals did not survive in dechlorinated Tayside tap water. In the artificial solution, populations of 50–100 animals survived without loss of activity for 6–8 weeks.

RESULTS

Figure 1 shows plots of the number of *Gammarus* affected by a given concentration of test substance against the logarithm of that concentration. For scores of 1 to 5 animals affected, an averaged concentration has been plotted and the number of observations and standard errors indicated. There is no possibility of a unique concentration for scores of 0 to 6, so each individual point has been entered. The numbers above the points indicate the number of separate experiments which gave that result. The concentrations of each compound required to affect 50% of the population of *Gammarus* (ED_{50}) have been estimated by up to three methods. These were: visual inspection, probit analysis [10] and the method of Waud [11]. Where all three were applied the agreement was within approx. 5% (the slight difference between the results given here and those presented in the preliminary communication [9] is the result of use of different methods of analysis). With the exception of 2-pentanone, the standard error for each ED_{50} value and the slope of the dose–response relationship have also been obtained by the method of Waud [11]. Table I gives the ED_{50}, standard error, slope and number of groups tested for each compound. Figure 2 gives plots of ln ED_{50} *v.* the number of methylene groups in the compound for each homologous series. Linear regression lines have been drawn through the points indicated and the characteristics of each line are given in the legend.

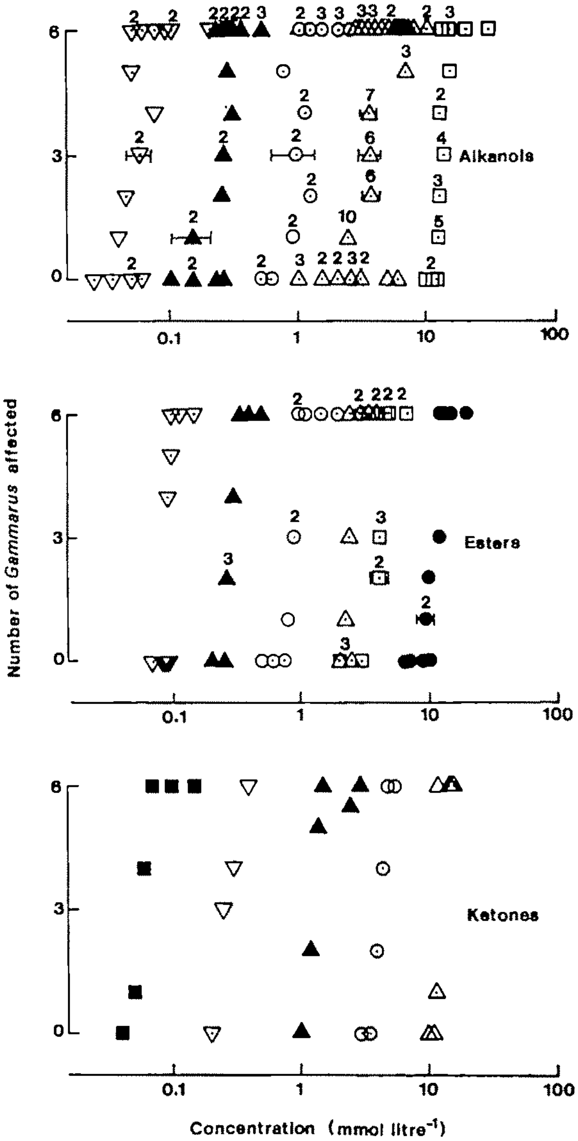

FIG. 1. Logarithmic dose–response relationships for n-alkanols, methylcarboxylic esters and n-alkyl ketones in *Gammarus*. Symbols are keyed to the number of carbon atoms in the main chain of the molecule: ● = 3 (propionate); ☐ = 4 (butyrate and butanol); △ = 5 (pentanoate, pentanol and pentanone); ⊙ = 6; ▲ = 7; ▽ = 8. Numbers above symbols = number of separate experiments on which result is based.

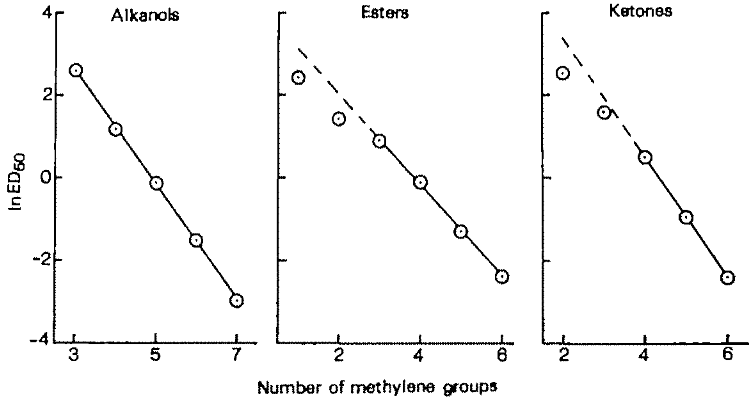

FIG. 2. The relationship between ln ED_{50} and number of methylene groups for n-alkanols, esters and ketones. Characteristics of linear regression lines: n-alkanols—$y = 6.723 - 1.377x$, $r^2 = 1.000$; esters—$y = 4.224 - 1.097x$, $r^2 = 0.999$; ketones—$y = 6.457 - 1.557x$, $r^2 = 1.000$.

DISCUSSION

Effects of n-alkanols

The relationship between ln ED_{50} for anaesthesia in *Gammarus* and n-alkanol chain length is linear, with no plateau around n-hexanol and n-heptanol. This contrasts with the results for inhibition of light emission by the water-soluble protein firefly luciferase, where the ED_{50} for n-heptanol is smaller than that for n-hexanol by a factor of only about 1.2, rather than the factor of > 3 observed with near homologues. Thus the diagnostic feature of the anaesthetic site proposed by Franks and Lieb [5] is not apparent in *Gammarus* and we must look elsewhere for further clues as to the physicochemical nature of the site.

TABLE I. *Anaesthetic potencies of n-alkanols, methyl carboxylic esters and n-alkyl ketones in* Gammarus

Compound	ED_{50} ± SEM (mmol litre^{-1})	Slope ± SEM	Number of groups tested
n-Alkanols			
Butanol	13.4±0.25	11±2	25
Pentanol	3.22±0.15	3±0.3	64
Hexanol	0.89±0.06	4±2	22
Heptanol	0.22±0.01	8±4	30
Octanol	0.052±0.003	5±2	19
Carboxylic esters			
Methyl propionate	11.3±0.33	13±8	12
Methyl butyrate	4.18±0.19	13±12	6
Methyl pentanoate	2.46±0.05	23±17	12
Methyl hexanoate	0.90±0.02	20±15	11
Methyl heptanoate	0.28±0.01	10±6	9
Methyl octanoate	0.094±0.001	76±63	10
n-Alkyl ketones			
2-Pentanone	12.5	/	6
2-Hexanone	4.23±0.13	20±7	6
2-Heptanone	1.26±0.05	19±17	6
2-Octanone	0.27±0.02	10±9	4
2-Nonanone	0.056±0.003	16±4	6

The *Gammarus* ED_{50} values for n-butanol to n-octanol decline by a factor of 4.0±0.15 (mean ± SEM) for each additional methylene group. This is an average value for the factor f given by:

$$f = \frac{\text{aqueous concn } x}{\text{aqueous concn } x+1} \qquad (1)$$

where x and $x+1$ are successive series members. f is a measure of the favourable interactions (that is, bonds) formed between a methylene group in the alkanol and the hypothesized site of action in the *Gammarus*, relative to the interactions formed in an aqueous environment. f can be expressed in terms of an energy difference between the case of a methylene group in *Gammarus* and a methylene group in water, by the following reasoning. If our measurements on *Gammarus* activity were made at equilibrium (and we believe they were), then there was an equilibrium between the concentration of alkanol in the aqueous phase and the concentration at our hypothesized site of action. This can be expressed as a partition coefficient, K, such that

$$K = \frac{\text{concn at site}}{\text{aqueous concn}} \qquad (2)$$

If K is greater than 1 (that is, greater concentration at the site of action) this is because the system comprising alkanol in the site of action is at a lower free energy level than the system consisting of alkanol in the aqueous phase. The change in free energy (ΔG) on transferring a mole of alkanol from water to the site of action is given by:

$$\Delta G = -RT \ln K \tag{3}$$

where R is the gas constant and T the absolute temperature (RT is 2.44 kJ mol^{-1} at 20 °C). The alteration in this free energy change on going from one series number to the next one up (for example n-hexanol to n-heptanol) is:

$$\Delta\Delta G = \Delta G(x+1) - \Delta G(x) \tag{4}$$

and is the result of changing the molecule by adding one methylene group. If we assume that the different parts of the alkanol molecule (methyl, methylene and hydroxyl groups) act independently, we are justified in equating $\Delta\Delta G$ with the decrease in free energy achieved by moving a methylene group on the alkanol from water to the site of action. Combining equations (3) and (4):

$$\Delta\Delta G = -RT(\ln K(x+1) - \ln K(x)) \tag{5}$$

and using equation (2) and rearranging:

$$\Delta\Delta G = -RT \ln \left\{ \frac{\text{concn } x+1 \text{ at site}}{\text{aqueous concn } x+1} \times \frac{\text{aqueous concn } x}{\text{concn } x \text{ at site}} \right\} \tag{6}$$

Assuming that equal biological activity is conferred by an equal concentration of alkanol at the site, then

$$\Delta\Delta G = -RT \ln \left\{ \frac{\text{aqueous concn } x}{\text{aqueous concn } x+1} \right\} \tag{7}$$

and, using equation (1):

$$\Delta\Delta G = -RT \ln f \tag{8}$$

An f value of 4 corresponds to a $\Delta\Delta G$ of -3.36 kJ mol^{-1}. We now have a number which is descriptive of the interaction between n-alkanol methylene groups and a site of anaesthetic action in *Gammarus* and we could hope that, by comparing the value in *Gammarus* with those obtained in other biological sites of action and in well-defined model systems, we would learn more about the nature of that site. Table II gives values of $\Delta\Delta G$ for the transfer of methylene groups from water (or very dilute aqueous media) to various sites of action or defined model systems and the values of f from which the $\Delta\Delta G$ were calculated. Only comparable chain length ranges have been considered. Where indicated, approximate corrections for temperature and ionic strength of the aqueous media have been made by applying the data of Aveyard and Mitchell [12] and Aveyard and Heselden [13].

The result for *Gammarus* is extremely close to that obtained for tadpoles by Meyer and Hemmi [3] and Pringle and colleagues [4]. It is also similar to that for suppression of luminescence in bacteria, which is interesting because it indicates a correlation between anaesthesia in *Gammarus* and inhibition of the activity of a bacterial (as opposed to firefly) luciferase. Well-defined model systems giving comparable free energies include hydrocarbons, dipalmitoyl phosphatidylcholine bilayers and alcohols themselves. Inhibition of axonal action potentials and their underlying ionic currents (a local anaesthetic action of alkanols) give values around -2.9 kJ mol^{-1}, slightly more positive than the -3.3 to -3.4 seen for general anaesthesia, but the one value for inhibition of synaptic transmission is equally different in the opposite direction at -3.7 kJ mol^{-1}. These comparisons extend those already drawn by Schneider [26], but are still not very helpful in defining the site of action of anaesthetics in *Gammarus*, simply because, as stated in the introduction with regard to the Meyer–Overton correlation, there are too many good models to choose from. However, the situation improves when the alkanol data are compared with those for the carboxylic esters.

Effects of carboxylic esters and n-alkyl ketones

The plots of ln ED_{50} *v.* number of methylene groups for esters and ketones are not as well fit by a straight line over the whole chain length range studied as are the n-alkanol data. Reasonable correlation coefficients are achieved ($r^2 = 0.989$ and 0.994 for esters and ketones, respectively), but these are improved (to 0.999 and 1.000) by assuming that the first two members deviate from linearity, as indicated in figure 2. If this deviation is artefactual it is difficult to explain, since the lower members of each series appear more potent than expected. It should be noted, however, that experiments using methyl propionate and butyrate took the longest time to come to steady state.

The value of f for the esters is considerably lower than that for the alkanols or ketones (regardless of the chain length range considered).

TABLE II. *The standard free energy of transfer of methylene groups, $\Delta\Delta G$, from an aqueous phase to biological sites of action and defined media as calculated from the factor f (see text). Temperature = 20 °C unless otherwise indicated. † Corrected for temperature; ‡ corrected for temperature and ionic conditions; †† not corrected, 6 °C and artificial sea water. DPPC = dipalmitoyl phosphatidylcholine; EPC = egg phosphatidylcholine*

System	f	$\Delta\Delta G$ (kJ mol^{-1})	Chain length range	Reference
Primary n-alkanols				
Reflex movement in *Gammarus*	4.0	−3.36	4–8	Present work
Reflex movement in tadpoles	4.0	−3.37	4,5,7,8	[3]
Righting response in tadpoles	3.8	−3.23	4,6,8	[4]
Immobilization of *Paramecium*	3.0	−2.67	4–8	[14]
Luminescence in bacteria	4.4	−3.59	4–8	[15]
Transmission of impulses through mammalian stellate ganglion:				
(1) Synaptic pathway	4.5	−3.69‡	4,5,8	[15]
(2) Non-synaptic pathway	3.2	−2.80‡	4,5,8	[15]
Sodium current in squid	3.5	−3.06‡	5–8	[8]
Potassium current in squid	3.2	−2.86‡	4–7	[16]
Compound action potential in toad	3.3	−2.91	4–8	[17]
Solubility in water	3.8	−3.28	5–8	[18]
Partition between water and hydrocarbon	3.9	−3.3	4–7	[12]
Partition between water and DPPC membranes	4.1	−3.45†	4–7	[19]
Partition between water and DPPC membranes	3.8	−3.23	5–8	[20]
Partition between water and EPC membranes	2.9	−2.61	5–8	[20]
Methyl carboxylic esters				
Reflex movement in *Gammarus*	2.6	−2.3	3–8	Present work
Reflex movement in *Gammarus*	3.0	−2.68	5–8	Present work
Sodium current in squid	2.8	−2.47††	5–8	[7]
Potassium current in squid	2.5	−2.27††	5,6,8	[9]
Solubility in water	4.8	−3.85	3,4	[21]
Carboxylic acids				
Solubility in water	4.9	−3.88	5–8	[18]
Partition between water and hydrocarbon	3.9	−3.30	4–7	[22]
n-Alkyl ketones				
Reflex movement in *Gammarus*	3.9	−3.33	5–9	Present work
Reflex movement in *Gammarus*	4.7	−3.80	7–9	Present work
Movement in tadpoles	4.0	−3.37	4,5	[23]
Sodium current in squid	3.1	−2.73††	6,9	[24]
Solubility in water	4.2	−3.52	5–7	[21]
Activity coefficient at infinite dilution in water	4.0	−3.37	3–7	[25]

This low value of f leads to a more positive $\Delta\Delta G$. Thus while $\Delta\Delta G$ for the alkanols is −3.4 kJ mol^{-1}, the most negative value for the esters is −2.7. The probability of obtaining this difference by chance is less than 0.05 (application of the Wilcoxon rank sum test to the individual f values between homologues). The least negative value for the ketones, obtained by fitting the whole chain length range, is −3.3, still significantly different from the most negative ester value ($P < 0.1$). The difference between n-alkanols and esters is also seen in their effects on the voltage-gated sodium and potassium currents in the squid giant axon (table II). This observation gives us the opportunity to refine our model of the anaesthetic site because we now need one which discriminates, albeit in a subtle manner, between esters and alkanols.

Models for sites of anaesthetic action in Gammarus

There are at least two hypotheses to accommodate the *Gammarus* anaesthesia data. The first is that there is a single site of action with different values of $\Delta\Delta G$ for alkanols (and ketones) and esters. Unfortunately, there is a distinct lack of data on the partition of methyl esters between water and model solvent or lipid phases [27]. Table II gives values of $\Delta\Delta G$ for transfer of methyl ester methylene groups between water and themselves, but the data are not extensive. The situation is rather better if one considers n-alkyl carboxylic acids, which are methyl esters without the methyl group, since Aveyard and Mitchell [22] have shown that $\Delta\Delta G$ for transfer of carboxylic acid methylene groups between water and hydrocarbons is the same as for n-alkanols. Similarly, studies using high pressure liquid chromatography show no difference between n-alkanols, ketones and carboxylic acids in absorption to a hydrophobic column [28, 29]. In fact, there is general agreement [8, 25, 27] that, as far as partition into a given bulk phase is concerned, a methylene group behaves in much the same way whatever the nature of the parent molecule. The hypothesized single site would, therefore, have to have rather special properties which should aid its identification.

The other hypothesis is that the n-alkanols and methyl carboxylic esters have subtly different sites of action, with the ester site providing a less favourable environment for methylene groups than that given in the alkanol site. This could reflect a difference in the chemical nature of the sites. Davis and co-workers [25] give "average" (over a range of compounds) values of $\Delta\Delta G$ for transfer of methylene groups from water to a range of solvents. The difference between the putative *Gammarus* alkanol site and that for esters is equivalent to the difference between toluene ("average" $\Delta\Delta G = -3.44\ \mathrm{kJ\ mol^{-1}}$) and nitrotoluene ("average" $\Delta\Delta G = -2.69\ \mathrm{kJ\ mol^{-1}}$). Alternatively, the difference could be primarily entropic, reflecting a more restricted environment for the esters [30]. Both of these sites could, of course, be on the same macromolecule or in the same lipid/protein environment.

CONCLUSION

The results of these studies indicate that, when the general anaesthetic potency of n-alkanols are measured in a single study, the data do not show a characteristic plateau around n-hexanol and n-heptanol. Therefore, the proposal by Franks and Lieb [5] that such a plateau could be used to refine models of the anaesthetic site is not supported. Instead, we suggest that further study of the differences between n-alkanols and methyl carboxylic esters, both in whole animals and in model phases, will increase our understanding of the nature of the site(s) of anaesthetic action.

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PREMEDICATION WITH SLOW RELEASE MORPHINE (MST) AND ADJUVANTS

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SUMMARY

Sixty-one women undergoing major gynaecological surgery received slow release morphine (MST) 60 mg, with placebo, hyoscine 0.6 mg or diazepam 10 mg, by mouth 2 h before surgery. Plasma morphine concentrations reached a steady level usually within 3 h after administration of MST, and did not increase after surgery unless supplementary opioid was given. Hyoscine delayed morphine absorption. Before operation no fewer than 50% of patients were sedated after MST alone, but this increased to 85% after MST and diazepam. Similarly, only the combination MST and diazepam produced anxiolysis. Postoperative mood was unhappier after MST and hyoscine. Emesis occurred in 40–57% of patients, and was not reduced by hyoscine. Therefore premedication with MST alone did not produce reliable sedation or anxiolysis. A combination of hyoscine and MST premedication cannot be recommended, as it did not produce sedation, anxiolysis or antiemesis and hyoscine may have delayed morphine absorption.

Opioids are used widely for premedication, as they produce sedation, contribute to balanced anaesthesia and provide postoperative analgesia. Slow release morphine (MST Continus) has been evaluated for preoperative use, as the convenience of the oral route is attractive and its duration of action is 7–12 h [1, 2]. Kay and Healy [3] found that MST 30 mg, given 2 h before operation, provided sedation and decreased postoperative pain, but they suggested that MST 60 mg might be a more suitable dose. Pinnock and colleagues [4] found that the response to premedication with MST 40 mg was similar to that of morphine 10 mg i.m., both given with atropine 0.6 mg i.m.

The present study was designed to evaluate the premedicant properties of MST 60 mg in women having major gynaecological surgery. MST alone was compared with MST with hyoscine 0.6 mg by mouth, to investigate the contribution of an anticholinergic drug to premedication and reduction in adverse effects. MST with diazepam 10 mg by mouth was also studied, as it was shown previously that MST alone did not produce anxiolysis [3, 4].

PATIENTS AND METHODS

Patient selection and observation

Ethics Committee approval was granted for the study which involved 61 women undergoing major gynaecological surgery. All patients were healthy (ASA I or II), aged 25–60 yr, and none was taking analgesic or psychotropic medication. Two hours before surgery, patients received oral premedication, comprising slow release morpine 60 mg with placebo (MST-P), hyoscine 0.6 mg (MST-H), or diazepam 10 mg (MST-D), in a double-blind randomized manner.

Patients were assessed and questioned by the anaesthetist before premedication, 1 h after premedication and in the anaesthetic room, before induction of anaesthesia, using the following rating scales. *Sedation*: 1 = alert and wide awake; 2 = awake but drowsy; 3 = asleep but easily roused; 4 = asleep not easily roused. *Anxiety*: 1 = completely calm; 2 = fairly calm; 3 = fairly nervous; 4 = very nervous. *Mood*: 1 = elated feeling; 2 = pleasant happy feeling; 3 = unhappy feeling; 4 = unpleasant, disturbed feeling. *Emesis*:

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1 = none; 2 = nausea; 3 = nausea and vomiting; 4 = repeated vomiting.

A standard anaesthetic was used which involved induction of anaesthesia with thiopentone 3–5 mg kg^{-1}, paralysis with a competitive neuromuscular blocking drug, tracheal intubation and ventilation of the lungs using 33% oxygen and 66% nitrous oxide, with 0.5% halothane if required. All patients received fentanyl (< 59 kg 0.1 mg, 60–80 kg 0.15 mg, > 81 kg 0.2 mg). Neuromuscular blockade was antagonized with atropine and neostigmine. The type and duration of surgery were noted. The same anaesthetist recorded sedation, anxiety, mood and emesis scores immediately after the patient was admitted to the recovery room, and at 1, 2 and 3 h after operation. *Pain* was assessed also at these times, using a 10-cm visual analogue score and a four-point rating scale: 1 = none; 2 = mild; 3 = moderate; 4 = severe.

Postoperative analgesia was given on demand as i.m. papaveretum (< 59 kg 10 mg, 60–80 kg 15 mg, > 81 kg 20 mg), and emesis was treated with prochlorperazine 12.5 mg i.m. The time of administration of the first dose of postoperative opioid was recorded.

Plasma morphine, catecholamine and cortisol measurement

Venous blood was sampled before induction of anaesthesia, in the recovery room and 2 h after surgery for measurement of morphine, catecholamine and cortisol concentrations. Blood samples were collected into heparinized glass tubes on ice, siliconized for morphine assay or containing EDTA and glutathione for catecholamine assay. Plasma was stored at −20 °C until required for assay.

Morphine was measured using a radioimmunoassay, with a prior liquid–solid extraction to reduce cross-reactivity with glucuronides. All results were expressed as morphine base, and the lowest limit of detection was 2–3 ng ml^{-1}. The mean deviation of measured values from standard values was 8.1%.

Plasma adrenaline and noradrenaline concentrations were measured using high performance liquid chromatography and electrochemical detection. Catecholamines were separated on a column using a mobile buffer, and extraction was performed using the method of Hjemdahl, Daleskog and Kahan [5]. A mixture of adrenaline, noradrenaline and dihydroxybenzylamine was used as an extracted standard, and dihydroxybenzylamine was used as an internal standard. The lowest limit of detection was 0.05 nmol $litre^{-1}$ for adrenaline and 0.10 nmol $litre^{-1}$ for noradrenaline. The intra-assay coefficient of variation was 11.0% for adrenaline and 6.7% for noradrenaline.

Plasma cortisol concentrations were measured using a radioimmunoassay kit (RIA U.K. Ltd), which used on antibody covalently bound to the inner surface of a polypropylene tube and ^{125}I-cortisol. The lowest limit of detection was 1.1 nmol $litre^{-1}$. The interassay coefficient of variation was 5.0% and the intra-assay coefficient of variation was 5.7%.

Statistics

Parametric data were analysed using the Pearson product moment correlation coefficient, *t* test, one-way analysis of variance for independent groups and two-way analysis of variance with repeated measures on one factor, followed by the Tukey test where appropriate.

Non-parametric data, including pain scores, were analysed using Chi-square and Kruskal–Wallis analysis of variance. Differences in sedation, anxiety and mood scores in each group, at each time, were analysed using the Mann–Whitney *U* test. Differences in scores before and after premedication were analysed using the Wilcoxon matched pairs signed ranks test.

RESULTS

The ages and weights of patients in the three groups were not significantly different. Fourteen patients received premedication more than 15 min early, and three patients received premedication more than 15 min late. The doses of thiopentone, fentanyl and the use of halothane were comparable in each group. The type and duration of surgery were similar in the three groups (table I).

Morphine absorption

Before induction of anaesthesia mean (SD) plasma morphine concentrations were not significantly different in patients who had received morphine on time (19.6 (6.3) ng ml^{-1}) compared with those who had not (19.9 (6.6) ng ml^{-1}). Plasma morphine concentrations in the anaesthetic and recovery rooms were not significantly different; however, plasma concentrations were lower after MST-H compared with MST-D

TABLE I. *Mean (SD) age and weight, details of surgery and mean (SD) time of first dose of postoperative opioid in each group MST-P = MST+placebo; MST-H = MST+hyoscine; MST-D = MST+diazepam. No significant difference between groups in age (f = 1.45) or weight (f = 1.63). No significant difference between groups in type (Chi square = 1.43) or duration (f = 1.04) of operation. No significant difference between groups in time of opioid administration after surgery (f = 0.04) or after premedication (f = 1.17)*

	MST-P ($n = 21$)	MST-H ($n = 20$)	MST-D ($n = 20$)
Age (yr)	44.1 (8.7)	42.5 (6.7)	39.9 (8.5)
Weight (kg)	62.9 (16.9)	68.4 (12.0)	64.0 (6.3)
Abdominal surgery	14	10	13
Vaginal surgery	7	10	7
Duration of surgery (min)	81.6 (30.3)	75.3 (22.7)	87.0 (30.0)
Time of first analgesia			
After surgery (h)	4.4 (23.0)	3.4 (14.8)	3.4 (7.3)
After premed. (h)	8.2 (23.8)	6.4 (11.6)	6.9 (7.3)

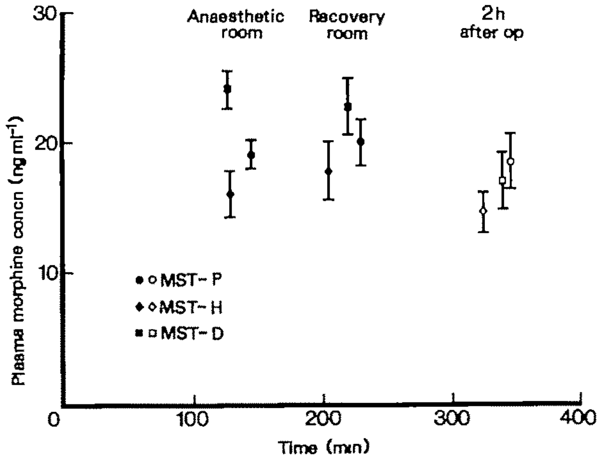

FIG. 1. Plasma morphine concentrations (mean ± SEM) at each time after premedication. Closed symbols show data from all patients (MST-P $n = 21$, MST-H $n = 20$, MST-D $n = 20$), open symbols show data from patients who had not received supplementary opioid at the time of the final blood sample (MST-P $n = 11$, MST-H $n = 8$, MST-D $n = 10$). Plasma morphine concentrations not significantly different at each time ($f = 0.11$). Plasma morphine concentrations significantly lower after MST-H compared with MST-D, in the anaesthetic and recovery rooms ($f = 5.78$, $P < 0.01$).

TABLE II. *Mean (SD) plasma morphine base concentrations (ng mg^{-1}) in 61 patients classified as awake or asleep. *Significantly greater than awake* (t = *2.04*, P < *0.05*)

	Awake	Asleep
Recovery room	18.6 (6.3)	20.6 (9.8)
2 h after op.	24.5 (18.1)	33.0 (17.1)*

($P < 0.01$) (fig. 1). Thirty-two patients required papaveretum during the first 2 h after surgery, before the third blood sample was obtained for morphine assay. Mean (SD) plasma morphine concentrations were significantly higher when i.m. opioid had been given (41.6 (15.8) ng ml^{-1}) compared with when it had not (16.9 (7.0) ng ml^{-1}) ($t = 7.8$, $P < 0.01$). Only one patient, who had received MST-H, showed an increase in plasma morphine without receiving i.m. opioid, from 7.8 ng ml^{-1} in the recovery room, to 19 ng ml^{-1} 2 h later.

Sedation

No patient was sedated before receiving MST and adjuvants, and all groups showed significant sedation after premedication and after operation ($P < 0.001$). One hour after premedication, more patients were sedated after MST-D (95%) compared with MST-P (62%) or MST-H (55%) ($P < 0.05$). There was no significant difference in sedation between the groups in the anaesthetic room: MST-P 62%, MST-H 60% and MST-D 85%. The number of patients sedated at both preoperative assessments was significantly greater after MST-D (85%) than MST-P (48%) and MST-H (35%) ($P < 0.05$). After operation there were no significant differences between the groups: MST-P 86%, MST-H 90% and MST-D 100%. Inadequate sedation occurred more often after MST-P and MST-H than after MST-D ($P < 0.01$), and oversedation occurred in four patients, two MST-P, one MST-H and one

MST-D. Sedation in the recovery room was not related to plasma morphine concentration; however, 2 h after operation morphine concentrations were greater in patients who were asleep compared with those who were awake ($P < 0.05$) (table II).

Anxiety

Before premedication, there were no significant differences in anxiety between the groups. Only MST-D patients showed significant anxiolysis in the anaesthetic room ($P < 0.001$); MST-D patients were less anxious than MST-P or MST-H ($P < 0.05$). Anxiety was reduced in all groups after surgery ($P < 0.05$).

Mood

A simple rating of happiness was used in the present study, but unhappy mood because of pain was specifically excluded. Mood scores before surgery were similar in the three groups but, after operation, patients were unhappier after hyoscine than after diazepam. Premedication did not significantly alter preoperative mood scores in any group. However, MST-H patients were unhappier than MST-D patients at 1 and 2 h after operation ($P < 0.05$). Unhappy mood was recorded significantly more often after MST-H compared with MST-D ($P < 0.01$) and MST-P ($P < 0.05$).

Emesis

The incidence of emesis was not significantly different in the three groups: 57 % MST-P, 45 % MST-H and 40 % MST-D patients suffered from nausea, vomiting, or both. There was no significant relationship between emesis and plasma morphine concentrations.

Pain

The ranked 10-cm visual analogue pain scores correlated well with the four-point ranking system ($r = 0.69$, $t = 14.4$, $P < 0.01$), and there was disparity between the two scoring systems on only 7.8 % occasions.

Analysis of pain scores showed that, at 1 and 2 h after operation, pain was reduced after MST-D compared with MST-H and, at 3 h, pain was reduced after MST-D compared with MST-H and MST-P ($P < 0.05$). Twenty-five percent of patients needed supplementary analgesia within 90 min, 52 % within 2 h and 69 % within 4 h. The time of first postoperative analgesia was not significantly different in the three groups (table I).

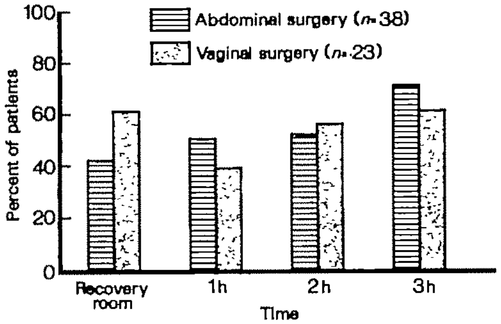

FIG. 2. Percent of patients at each time, after abdominal or vaginal surgery, with no pain or mild pain.

The type of surgery had no effect on postoperative pain: pain scores were not significantly different during the first 3 h after abdominal or vaginal operations (fig. 2). Severe pain occurred in only 17 % patients after vaginal surgery, and 18 % patients after abdominal surgery. The mean (SD) time to administration of the first supplementary opioid was not significantly different after vaginal surgery (4.6 (2.9) h), compared with abdominal surgery (3.1 (4.7) h). Surprisingly, the present study showed that pain was not significantly different after abdominal or vaginal surgery. Nearly 30 % of the patients did not require supplementary analgesia within the first 4 h after surgery, which was approximately 7 h after premedication. Patients who had received MST and diazepam seemed to complain of less pain than the other two groups; this was not related to increased sedation.

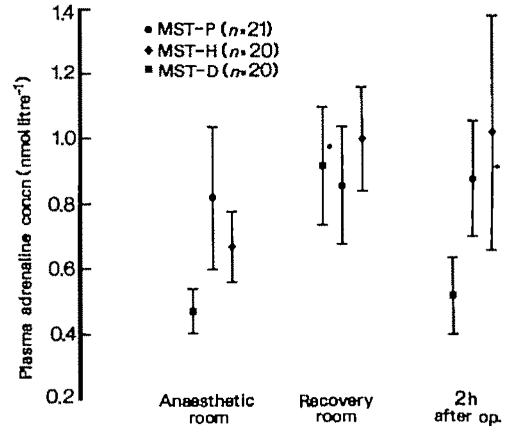

FIG. 3. Plasma adrenaline concentrations (mean ± SEM) increased in the recovery room compared with in the anaesthetic room, in all three groups ($f = 3.5$, $P < 0.05$). No significant differences between the three premedication regimens.

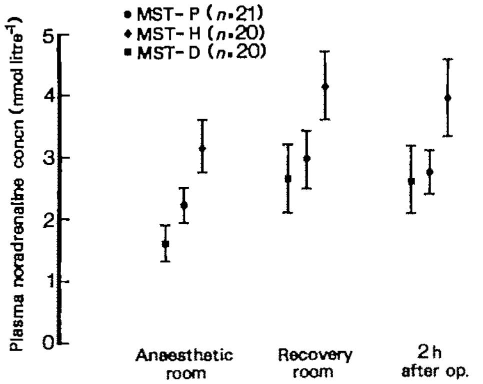

FIG. 4. Plasma noradrenaline concentrations (mean ± SEM) increased in the recovery room and after operation in all three groups ($f = 5.08$, $P < 0.01$). Noradrenaline concentrations were reduced after MST-D compared with MST-H ($f = 3.19$, $P < 0.05$).

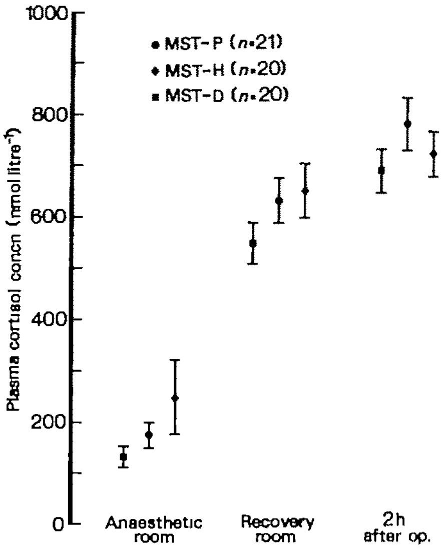

FIG. 5. Plasma cortisol concentrations (mean ± SEM) increased, in all three groups, in the recovery room and after operation ($f = 158.6$, $P < 0.01$).

Catecholamine concentrations

Plasma adrenaline concentrations were not significantly different after the three premedication regimens (fig. 3). Overall plasma adrenaline concentrations increased in the recovery room compared with in the anaesthetic room ($P < 0.05$); however, there was no significant difference between adrenaline concentrations in the recovery room and at 2 h after surgery. In the three groups plasma noradrenaline concentrations increased in the recovery room, at 2 h after operation ($P < 0.01$). Plasma noradrenaline concentrations were lower after MST-D compared with MST-H ($P < 0.05$) (fig. 4). Postoperative adrenaline and noradrenaline concentrations were greater in patients who were asleep compared with those who were awake ($P < 0.05$).

Plasma catecholamine concentrations were not related to anxiety, mood, pain or plasma morphine concentrations.

Cortisol concentrations

Plasma cortisol concentrations increased in the recovery room and after operation, compared with values in the anaesthetic room ($P < 0.01$), but there was no significant difference in cortisol concentrations between the three groups (fig. 5).

Plasma cortisol concentrations were not related to plasma morphine concentrations, pain, sedation or anxiety.

DISCUSSION

The perioperative use of MST is not now recommended, because of concern regarding delayed absorption of morphine in the presence of decreased gastric emptying, produced by pharmacological or pathological causes [6]. The present study, commenced early in 1984, has shown that one preoperative dose of MST, given to healthy patients, was absorbed well and that the timing of its administration was not critical. If supplementary opioid was not needed, plasma morphine concentrations remained fairly stable throughout the study period. Peak plasma morphine concentrations were reached in the anaesthetic or recovery room in all but one patient, who had received MST and hyoscine and in whom plasma morphine concentration increased at 2 h after operation. Perhaps the anticholinergic drug had slowed gastric emptying sufficiently to delay morphine absorption from the small intestine. In support of this hypothesis, patients who received MST and hyoscine had lower preoperative plasma morphine concentrations than those who received MST and diazepam. Preoperative anxiety decreases gastric emptying [7], therefore anxiolysis following diazepam may have promoted morphine absorption, whilst gastric stasis following hyoscine may have had the opposite effect.

Forty-eight percent of patients did not receive further analgesia before blood was sampled 2 h after operation. Plasma morphine concentrations were not increased in these patients, approximately 5 h after MST administration, remaining stable after surgery, therefore the use of supplementary i.m. opioid appeared to be safe in this group of patients. However, a marked increase in plasma morphine concentration occurred after i.m. papaveretum.

The present study confirmed previous observations of significant sedation when MST premedication was administered [3, 4]. However, although sedation occurred in all three groups, the addition of diazepam to MST produced more predictable results, with 85% of patients sedated at both assessments. As fewer than 50% of the patients were drowsy or asleep at 1 and 2 h after MST alone or with hyoscine, these regimens cannot be recommended. Postoperative sedation was shown to be associated with higher plasma morphine and catecholamine concentrations. Increased catecholamine concentrations may have been associated with pain, which resulted in the administration of supplementary opioid and consequent sedation.

Anxiety is difficult to measure, and several scoring systems have been used before operation. In the present study, a four-point rating scale was chosen for simplicity and brevity. A predictable postoperative reduction in anxiety [8] was detected, suggesting that the rating system was sensitive to acute changes. Reduction of apprehension is an important feature of good premedication, and the lack of anxiolysis after MST alone, shown previously [3, 4], was confirmed in the present study. It was also demonstrated that the addition of hyoscine to MST did not improve anxiolysis, whereas diazepam was effective. Overall, unhappy mood was seen more often after MST and hyoscine than after MST alone or with diazepam.

It has been suggested that postoperative emesis occurs in 20–40% of all surgical patients [9]; however, in the present study, 57% of patients suffered from nausea and vomiting after MST and placebo. The occurrence of emesis was not related to plasma morphine concentrations. Hyoscine premedication has been shown to reduce postoperative emesis [10], but its duration of action is short; the failure of hyoscine to reduce nausea and vomiting significantly in the present study may therefore have been a result of the prolonged action of MST.

In conclusion, sedation was unpredictable and there was no anxiolysis when MST alone was used before operation; the addition of diazepam was necessary to improve the quality of premedication. The use of hyoscine with MST cannot be recommended, as it did not improve sedation, worsened mood and did not decrease the rather high incidence of emesis; it may also have delayed the absorption or morphine.

(Since 1984 the perioperative use of MST has not been recommended by the manufacturers (Napp Laboratories).)

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SUBARACHNOID ANAESTHESIA PRODUCED BY HYPERBARIC LIGNOCAINE IN ELDERLY PATIENTS

Prolongation of Effect with Adrenaline

J. P. RACLE, A. BENKHADRA AND J. Y. POY

SUMMARY

The effects of adrenaline on the duration of spinal anaesthesia induced with hyperbaric lignocaine were investigated in 60 elderly patients in a double-blind study. Each patient received 5% lignocaine 2 ml in 7.5% dextrose to which was added physiological saline 1 ml, 1:1000 adrenaline 0.2 ml (0.2 mg) plus normal saline 0.8 ml, or adrenaline 0.4 ml with normal saline 0.6 ml. The duration of sensory block (measured by two- and four-segment regression times, and times to regression to T12 and L2 dermatomes) was prolonged significantly by both doses of adrenaline. The addition of adrenaline also produced a significant increase in the duration of complete motor block.

Adrenaline is commonly used to prolong the duration of subarachnoid anaesthesia, but its efficacy is controversial when hyperbaric lignocaine is used. In a double-blind trial, Chambers and colleagues [1] found that adrenaline 0.1–0.3 mg did not produce a meaningful prolongation of duration. One criticism of this study [2] was that the population studied was older than in previous studies, but the results of Spivey [3] in term parturients substantiated those of Chambers and colleagues. There is no general agreement, however, because Leicht and Carlson [4] showed that adrenaline 0.3 mg significantly increased both the time for two-segment regression and the time to regression to T12. Therefore, the present study was undertaken in elderly subjects to assess a possible effect of adrenaline on the duration of the subarachnoid anaesthesia produced by hyperbaric lignocaine.

PATIENTS AND METHODS

Sixty patients older than 75 yr (ASA categories II and III), undergoing repair of an inguinal hernia in the supine position, gave informed consent after detailed explanation of the procedure. The patients were randomly allocated to one of three groups according to the permutation table of Cochran and Cox. Group I ($n = 20$) received 5% lignocaine 2 ml in 7.5% dextrose with 0.9% sodium chloride 1 ml (i.e. 100 mg of 3.33% lignocaine solution in 5% dextrose). Group II ($n = 20$) received 5% lignocaine 2 ml in 7.5% dextrose with 1:1000 adrenaline 0.2 ml (0.2 mg) and 0.8 ml of physiological saline solution. Group III ($n = 20$) received 5% lignocaine 2 ml in 7.5% dextrose with adrenaline 0.4 ml (0.4 mg) and physiological saline solution 0.6 ml. The adrenaline and physiological saline were added at the time of injection. Patient characteristics are shown in table I.

Premedication was with flunitrazepam 0.5–1 mg by mouth about 90 min before the induction of anaesthesia. Immediately before induction of anaesthesia, an 18-gauge cannula was inserted to an arm vein, and 300 ml of lactated Ringer's solution was infused. This was repeated after the injection of the spinal anaesthetic. The patient was placed in the lateral decubitus position, on a horizontal operating table. Under aseptic conditions, lumbar puncture was performed with a 22- or 19-gauge spinal needle at the L3-4 intervertebral space using either a midline or a paramedian approach. All injections were made at a rate of about 1 ml over 4–5 s and all solutions

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TABLE I. *Clinical data of the patients (mean ± SD).* n = *20 in each group. No statistically significant differences between groups (one-way analysis of variance)*

	Group I (lignocaine + normal saline)	Group II (lignocaine + adrenaline 0.2 mg)	Group III (lignocaine + adrenaline 0.4 mg)
Sex (F/M)	12/8	9/11	7/13
Age (yr)			
Mean	78±5	81±7	78±5
Range	75–91	75–97	75–92
Weight (kg)			
Mean	63±14	62±14	65±14
Range	47–110	35–98	45–96
Height (cm)			
Mean	164±9	164±9	164±9
Range	148–190	154–180	152–188

were at room temperature. Immediately after the injection, the patient was placed in the supine horizontal position for the duration of surgery.

The time of completion of the injection of the local anaesthetic solution was used as the basis for the measurement of all time intervals. The level of sensory block was evaluated bilaterally in the mid-clavicular line, on the perineum and on the legs, by pinching with a Pean forceps at 2-min intervals for 30 min and, thereafter, at 15-min intervals until no sensory loss could be detected. Sensory blockade was considered complete when the patient did not respond when the forceps was closed to its first ratchet [5]. When the levels of blockade were unequal on the two sides, the higher was used for statistical purposes. Motor blockade was assessed at the same time as sensory block using the criteria described by Bromage [6]: 0 = no impairment of movement of legs or feet; 1 = barely able to flex knees, no impairment of movement of feet; 2 = unable to flex knees, barely able to move feet; 3 = unable to move feet or knees. The times to recovery from blockade in the two and four uppermost segments, and to recovery at the T12 and L2 dermatomes were noted. Test procedures were performed by two specially trained anaesthetic nurses who were unaware of the nature of the study and were not present at the time of injection.

Arterial pressure and heart rate (Dinamap, Critikon) were measured at 2.5-min intervals throughout anaesthesia and surgery, and at intervals of 15-min during recovery. The ECG was monitored continuously using lead CM5 configuration during induction of anaesthesia and surgery. Hypotension was treated with i.v. fluid. If this did not prevent a decrease in systolic arterial pressure of greater than 20% of the resting figure, ephedrine 15–30 mg i.v. was given. Resting arterial pressure was determined during the preoperative visit on the day before surgery [7]. When the clinical condition permitted, and with the return of active lower limb movements, the patient was returned to the surgical ward and kept supine for 12 h.

All data are presented as means ± standard deviation (SD), together with medians and ranges. Median values of ordinal data were compared using the Kruskal–Wallis test. Mean values of quantitative data were compared using one-way analysis of variance (ANOVA) and appropriate Student's test.

RESULTS

There were no significant differences between the three groups in regard to sex, age, weight and

TABLE II. *Characteristics of sensory block in the three groups studied (mean ± SD). Statistical significance tested by one-way analysis of variance and appropriate Student's* t *test. Group II and III* v. *group I:* **P < *0.01;* ***P < *0.001*

	Group I	Group II	Group III
Highest level of analgesia			
Median	T9–T8	T7	T7
Range	T10–T2	T10–T2	T10–T3
Time from injection to highest level (min)			
Mean	7.8±3	8.5±3	9.4±3
Range	4–14	4–12	4–16
Time for two-segment regression (min)			
Median	60	90	90
Mean	55±15	80±24**	84±34**
Range	30–90	45–120	40–150
Time for four-segment regression (min)			
Median	75	110	115
Mean	74±18	105±33**	110±40**
Range	45–120	60–180	50–170
Time for regression to T12 (min)			
Median	60	100	120
Mean	65±12	110±39***	126±35***
Range	30–80	60–210	60–180
Time for regression to L2 (min)			
Median	90	130	150
Mean	88±13	144±42***	154±33***
Range	50–105	75–240	90–210

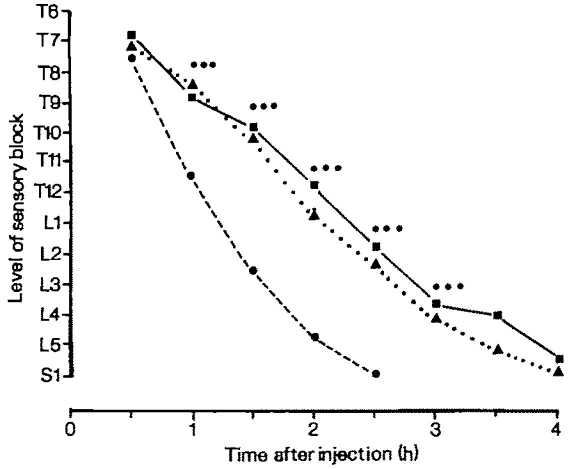

FIG. 1. Mean duration of sensory blockade after spinal analgesia with lignocaine 100 mg in 5% dextrose with: normal saline (group I, ●), adrenaline 0.2 mg (group II, ▲) and adrenaline 0.4 mg (group III, ■). Statistical significance tested by one-way analysis of variance and appropriate Student's *t* test. Group II and III *v.* group I: ***$P < 0.001$.

TABLE III. *Characteristics of motor block in the three groups studied (mean ± SD). Statistical significance tested by one-way analysis of variance and appropriate Student's* t *test. Group II and III* v. *group I:* ***$P < 0.001$

	Group I	Group II	Group III
Time to onset of total motor block (grade 3) (min)			
Mean	4.3±1	4.1±2	3.8±2
Range	2–6	2–8	2–10
Duration of grade 3 motor block (min)			
Median	75	120	140
Mean	74±14	131±35***	148±36***
Range	50–105	60–210	70–230
Duration of grade 2 motor block (min)			
Median	80/90	150	160
Mean	89±19	151±37***	163±37***
Range	60–130	80–240	80–240
Duration of grade 1 motor block (min)			
Median	110	170	180
Mean	109±19	173±41***	179±39***
Range	90–140	100–270	90–250

TABLE IV. *Systolic arterial pressure (SAP) and i.v. fluid administration (volume of lactated Ringer's solution given) (mean ± SD)*

	Group I	Group II	Group III
Resting SAP (mm Hg)			
Mean	139±21	148±21	152±23
Range	100–180	120–200	110–200
Lowest SAP (mm Hg)			
Mean	109±26	112±19	112±26
Range	40–175	90–170	60–164
Mean % of resting values	−22±15	−24±10	−26±16
Ringer's solution (ml kg^{-1})			
Mean	10±4	12±6	13±5
Range	5–20	7–28	7–25

height (table I). Median maximal levels of blockade (T9–T7) were similar in the three groups (table II). Although the time to maximal segmental level varied greatly in all groups (range 4–16 min) the mean values did not differ significantly. The time for regression of the level of blockade by two sensory dermatomes was significantly greater in groups II and III (+46% and +53%, respectively). The mean time for the sensory block to regress by four segments below the maximum was significantly prolonged with the addition of adrenaline 0.2 or 0.4 mg (+42% and +49%, respectively). Compared with group I, the mean time for regression of the level of blockade to T12 was significantly longer in group II (+45 min, +69%) and in group III (+61 min, +94%). Time to regression to L2 was also significantly longer with the addition of adrenaline (+64% and +75%, respectively). After the first 1 h, there was a significant difference in the segmental regression between lignocaine with adrenaline and lignocaine with physiological saline solution (fig. 1). There was no significant difference between groups II and III with regard to two- and four-segment regression or regression to the T12 or L2 level (table II, fig. 1).

The onset and duration of the three degrees of motor blockade are shown in table III. All patients developed complete motor block in the legs, and this was obtained in all groups in a mean time of about 4 min (range 2-10 min). Significant differences in duration of grade 3 motor block were found between groups II and III and group I (+77% and +100%, respectively). The duration of grade 2 and grade 1 motor blockade also increased with administration of adrenaline.

Resting systolic arterial pressure did not differ significantly between the groups (table IV). The mean maximal decreases in systolic arterial pressure from the resting values were between 22 and 26%. Ten patients in group I, nine in group II and 12 in group III received ephedrine because of hypotension. No statistically significant difference was noticed between the groups in the amount of i.v. fluids given. Analgesia was considered to be satisfactory in all patients because no supplementation with i.v. or inhalation anaesthesia was required for pain during surgery. No postoperative headache was noticed in the reports from the nurses on the surgical unit.

DISCUSSION

Lignocaine was chosen because this local anaesthetic produced satisfactory spinal anaesthesia for patients undergoing surgery of the lower trunk of short duration. Large gauge spinal needles were used because advanced hypertrophic osteoarthritis of the vertebral column is frequent in elderly patients.

The present study showed that the addition of adrenaline 0.2 or 0.4 mg to lignocaine appeared to produce clinically useful prolongation of spinal anaesthesia. These results are in agreement with those of Leicht and Carlson [4] who found that adrenaline 0.3 mg significantly prolonged the time for regression to T12 by an average of 31%. In man, adrenaline was found to decrease plasma lignocaine concentration [8]. However, Chambers and colleagues [1] found no prolongation of two- and four-segment regression time when adrenaline 0.1, 0.2 or 0.3 mg was added to 5% lignocaine 1.5 ml in 7.5% dextrose. They reported an increase only in times until no analgesia or anaesthesia was detectable in the adrenaline groups. Denson and others [9], using a rhesus monkey model, also reported no prolongation of lignocaine-induced spinal sensory blockade by adrenaline 0.2 mg. In term parturients undergoing Caesarean section, Spivey [3] reported no increase in duration of spinal anaesthesia, measured by the time for two-segment regression, when adrenaline 0.2 mg was added to hyperbaric lignocaine.

The discrepancy between the present study and that of Chambers and colleagues [1] could be explained by differences in methodology. In these two studies, a wide variability of duration was noted among patients who received the same drug dose or combination. Predictability was not good: in some patients receiving added adrenaline duration of action was less than the mean for the plain solution. Taking into account this individual variation in response, it may be necessary to include more than 10 in each study group in order to show statistically significant effects. The difference in findings may also result from the subjective nature of the method used to determine the sensory level of blockade, but pinching with a forceps was taken by Moore [10] to be equivalent to pinprick and seems more reproducible in elderly patients. It is surprising that, in Chambers' study, mean cephalad spread of blockade and the times for two- and four-segment regression should have been greater in patients who received no adrenaline. As Leicht and Carlson [4] pointed out, the baricity of the local anaesthetic solutions differed in Chambers' groups because each group received a different volume of adrenaline. Furthermore, the concentration of lignocaine was greater in Chambers' control group than in the study groups. In the present study, the concentration of lignocaine was constant, and each patient received an equal volume of anaesthetic solution.

One criticism of the present study might be that all the patients received the same dose of lignocaine (100 mg in 3 ml), regardless of their height, but there was no significant difference in mean height between the groups, and there have been no controlled studies on the effect of patient height on distribution of spinal anaesthetic solution [11].

Denson and co-workers evaluated lignocaine 30 mg with adrenaline 0.2 mg in monkeys placed in a sitting position. In spite of similarities between humans and primates in sensory and motor responses to spinal anaesthesia [13], accurate evaluation of sensory responses in monkeys may not always be possible, as noted by Vaida and others [12].

It is difficult to compare the effect of adrenaline on the duration of blockade between pregnant and non-pregnant patients. In term parturients [3] the use of a low dose of local anaesthetic (lignocaine 40 mg) resulted in too high a block. However in "high thin blocks", the maximum level of blockade decreased more rapidly than a comparable but more dense sensory level achieved with a larger dose. Thus one can postulate that not only the dose, but also the concentration of both local anaesthetic and vasoconstrictor influence the duration of the spinal block. It seems that, after the intrathecal injection of adrenaline, a concentration gradient develops with a progressive decrease in vasoconstrictor concentration away from the site of the injection. This could explain why adrenaline prolonged sensory blockade in the lower thoracic and lumbar segments for a longer period than in upper thoracic segments. Kozody and others [14] demonstrated in dogs that lignocaine 100 mg administered intrathecally increased lumbosacral cord blood flow by an average of 138% at 40 min, but did not alter cervical or thoracic cord blood flow. This increase was prevented by the addition of adrenaline 0.2 mg to intrathecal lignocaine.

In older patients, arterial hypotension was more common than in younger ones during spinal anaesthesia [15]. Thus, it might be expected that the combination of adrenaline and hypotension in elderly patients could be associated with a risk of anterior spinal artery thrombosis. In this respect, great care was needed in preventing or treating hypotension.

In conclusion, the results of this study confirm that adrenaline 0.2 mg or 0.4 mg added to hyperbaric lignocaine prolongs significantly the duration of spinal anaesthesia in elderly patients.

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HIGH SPINAL NERVE BLOCK FOR LARGE BOWEL ANASTOMOSIS

A Prospective Study

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AND A. R. AITKENHEAD

SUMMARY

In a randomized, prospective study of patients undergoing large bowel anastomosis, 47 patients received subarachnoid block and light general anaesthesia, and 51 received conventional general anaesthesia with intermittent positive pressure ventilation. Anastomotic dehiscence occurred in 17.0% of the spinal group and in 17.6% of patients anaesthetized by the conventional technique. Blood loss was significantly (P < 0.001) lower in the spinal group than in the general anaesthesia group. Blood transfusion was required in 10.6% of patients in the spinal group and 21.6% of patients receiving general anaesthesia.

Spinal nerve block is theoretically beneficial for patients undergoing large bowel surgery, because of profound relaxation of the abdominal wall, contraction of the bowel and reduced bleeding which provide good operating conditions. Blood flow to the colon is increased by spinal nerve block [1] and it is known that the blood supply to a colonic anastomosis is an important factor in promoting anastomotic healing in the colon [2, 3]. Hypovolaemia and blood transfusion increase the risk of anastomotic breakdown [4, 5] and long-term survival from carcinoma of the colon or rectum is reduced in patients who received blood transfusion at the time of surgery [6–8]. The use of spinal nerve block may obviate the necessity for using neostigmine, which has undesirable effects on bowel contractility and blood flow [9, 10].

In a retrospective study of 94 large bowel anastomoses, Aitkenhead, Wishart and Peebles Brown [11] found that 23.1% of patients receiving conventional general anaesthesia suffered anastomotic dehiscence, compared with only 7.4% of patients who received subarachnoid or extradural spinal nerve block, although this difference was not statistically significant. Blood loss was lower in patients receiving spinal nerve block. The present prospective study was designed to determine if the trend suggesting improved outcome in patients who received spinal nerve block could be confirmed.

PATIENTS AND METHODS

Ninety-eight patients scheduled consecutively for large bowel anastomosis were allocated from a random selection chart to receive either high spinal nerve block with light general anaesthesia (group A) or "conventional" general anaesthesia involving neuromuscular blockade (group B). All anaesthetics were administered by the same anaesthetist (H.Y.W.).

Bowel preparation and surgery

During the initial period of the study, the antibiotic regimen consisted of succinylsulphathiazole and neomycin administered by mouth for 5 and 2 days before operation, respectively; during the latter part of the study, gentamicin and metronidazole were administered i.v. at the time of premedication and for 36 h after operation. In all patients, bowel wash-out was performed on the evening before surgery. Each

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anastomosis was constructed using a two-layer inverting technique, with continuous catgut for the inner layer and interrupted black silk for the outer layer. All but three of the operations were performed by the same surgeon (D.P.B.).

Anaesthetic technique

Patients received premedication comprising papaveretum 10–20 mg and hyoscine 0.2–0.4 mg (group A $n = 14$; group B $n = 19$), pethidine 25–50 mg, promethazine 12.5–25 mg and hyoscine 0.2–0.4 mg (group A $n = 19$; group B $n = 18$) or cyclizine 50 mg and morphine 10–15 mg (Cyclimorph) (group A $n = 14$; group B $n = 14$).

Group A. Anaesthesia was induced using thiopentone 4–5 mg kg^{-1}. After administration of suxamethonium 25–50 mg, the larynx was sprayed with 10% lignocaine and the trachea intubated. Anaesthesia was maintained using 0.5% halothane in a mixture of 50% nitrous oxide in oxygen, with the patient breathing spontaneously. Subarachnoid block was performed immediately after induction of anaesthesia, with the patient in the lateral position. Injection was made at the L3–4 or L4–5 space using a 22-gauge spinal needle. Cinchocaine 0.5% in 6% dextrose, 2.25–3 ml, or 1% amethocaine in 5% dextrose, 1.25–1.5 ml, was injected with minimal barbotage. The patient was then placed supine and head down; the intention was to obtain a sensory block to the level of T4–5.

Group B. After induction of anaesthesia with thiopentone 4–5 mg kg^{-1}, pancuronium 4–6 mg was administered and anaesthesia was maintained using 67% nitrous oxide and 0.5% halothane in oxygen supplemented with morphine 10 mg i.v. At the end of the procedure, residual neuromuscular blockade was antagonized with atropine 1.2 mg and neostigmine 2.5 mg, administered together.

Systolic arterial pressure was measured using an oscillotonometer, and blood loss was estimated by weighing swabs and measuring the contents of suction bottles.

Postoperative analgesia was provided by i.m. morphine. Anastomotic breakdown was detected using the following criteria [12]:

(1) Escape of flatus or faeces through the wound, drain site or vagina.

(2) Anastomotic dehiscence demonstrated at subsequent laparotomy or postmortem.

(3) Local abscess formation when subsequent events suggested anastomotic breakdown as the cause.

Barium enema was performed when anastomotic rupture was suspected clinically, but was not used routinely. Statistical analysis was carried out using Student's *t* test, Wilcoxon rank sum test or Chi square test with Yates' correction, as appropriate.

RESULTS

There were no significant differences between groups with respect to type of surgery (table I). There were significantly more patients in group B who underwent repair of the colon following removal of a rectal polyp (table II).

Mean (± SD) ages of patients in each group were comparable: group A 53.3 ± 18.6 yr; group B 53.3 ± 19.3 yr. There were no significant differences between groups in respect of preoperative haemoglobin concentration (group A: 13.4 ± 1.5 g dl^{-1}; group B: 13.0 ± 1.3 g dl^{-1}) or duration of

TABLE I. *Operation. Number of patients (percentage of the total,* n) *in each group*

Operation	Group A ($n = 47$)	Group B ($n = 51$)
Sigmoid resection	11 (23.4)	9 (17.6)
Right hemicolectomy	9 (19.1)	9 (17.6)
Subtotal colectomy	6 (12.8)	10 (19.6)
Resection of terminal ileum and caecum	6 (12.8)	5 (9.8)
Anterior resection	6 (12.8)	4 (7.8)
Resection of transverse colon	6 (12.8)	2 (3.9)
Left hemicolectomy	2 (4.3)	6 (11.8)
Ileo–transverse anastomosis	1 (2.1)	4 (7.8)
Rectal polypectomy	0	1 (2.0)
Ileo–descending anastomosis	0	1 (2.0)

TABLE II. *Pathology. Numbers of patients (percentage of the total,* n) *in each group.* *$P < 0.05$

Pathology	Group A ($n = 47$)	Group B ($n = 51$)
Carcinoma	23 (48.9)	19 (37.3)
Crohn's disease	15 (31.9)	13 (25.5)
Diverticulitis	4 (8.5)	4 (7.8)
Atonic bowel	3 (6.4)	5 (9.8)
Polyp	0	6 (11.8)*
Volvulus	0	2 (3.9)
Faecal fistula in appendicectomy scar	1 (2.1)	0
Stitch granulomata	1 (2.1)	0
Obstruction from radiation adhesions	0	1 (2.0)
Haemangioma	0	1 (2.0)

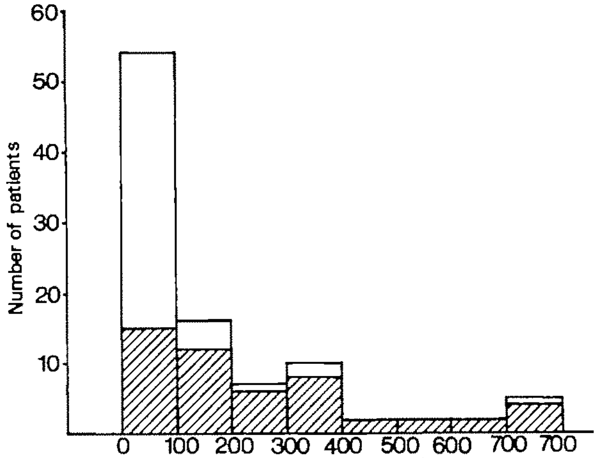

FIG. 1. Distribution of estimated intra-operative blood loss in patients undergoing colonic surgery under subarachnoid spinal nerve block (open boxes) or conventional general anaesthesia (cross-hatched boxes).

surgery (group A: 75±22 min; group B: 71±20 min).

The mean (±SD) maximum reduction in systolic arterial pressure from its preoperative value was significantly greater in group A (51.0±10.4%) than in group B (11.6±17.0%) ($P < 0.001$).

Blood loss was 105±250 ml in group A, and 288±288 ml in group B ($P < 0.001$) (fig. 1). No patient received blood transfusion during surgery. In group A, 10.6% of patients received blood transfusion in the postoperative period, compared with 21.6% in group B ($P > 0.05$).

The mean duration of i.v. infusion was 4–5 day and most patients started to receive oral fluids within 48 h; there were no differences between groups. Analgesic requirements were similar in each group: on average three or four doses of i.m. morphine were administered in the first 24 h. There were no differences between groups in relation to the incidence of wound infection or the mean duration of stay in hospital (19 days).

Anastomotic breakdown was diagnosed in 17.0% of patients in group A and 17.6% of patients in group B. The outcome after anastomotic breakdown (table III) was similar in the two groups. There were no differences in the incidence of anastomotic breakdown before and after the change of antibiotic regimen, and no difference related to the drugs administered for premedication.

TABLE III. *Outcome after anastomotic breakdown. Numbers of patients (percentage of the total,* n) *in each group*

Outcome	Group A ($n = 47$)	Group B ($n = 51$)
Settled with conservative treatment	5	6
Reoperated	2	2
Died following breakdown	1	1
Total	8 (17.0)	9 (17.6)

TABLE IV. *Mortality. Numbers of patients (percentage of the total,* n) *in each group*

Cause of death	Group A ($n = 47$)	Group B ($n = 51$)
Related to anastomotic breakdown	1	1
Pulmonary thromboembolism	2	0
Bronchopneumonia, carcinomatosis	2	0
Total	5 (10.6)	1 (2.0)

Two patients in group A developed ventilatory insufficiency during surgery; this occurred at 20–25 min after performance of subarachnoid spinal nerve block, and spontaneous breathing returned after 60 min. Ventilation was controlled during the period of insufficiency. One patient in group A suffered a severe headache which lasted from the 3rd to the 7th days after operation, and the same patient developed diplopia on the 7th day.

Three patients were thought to have clinical evidence of deep venous thrombosis (two in group A, one in group B), and all three received therapeutic doses of heparin.

Five patients in group A and one in group B died. The causes of death are listed in table IV. Two of the deaths (one in each group) were consequences of ruptured anastomosis. Both patients in group A who had clinical evidence of deep venous thrombosis died of pulmonary thromboembolism. The remaining two deaths (both in group A) were unrelated to surgery or anaesthetic technique. The difference between groups in respect of total mortality is not statistically significant ($P > 0.15$).

DISCUSSION

This prospective study has demonstrated a similar incidence of anastomotic dehiscence in patients who received spinal nerve block or general anaesthesia involving neuromuscular blockade. There were no differences between groups in respect of postoperative analgesic requirements, duration of i.v. fluid therapy or duration of stay in hospital. Most of the theoretical advantages of spinal nerve block in patients undergoing large bowel anastomosis [13] were not realized. The incidence of anastomotic breakdown in this study was comparable to that reported elsewhere [11, 14–16). Although a larger absolute number of patients in group A developed deep vein thrombosis, it is inappropriate to draw any conclusions on its aetiology, as the numbers were small, and only clinical signs were used for its detection.

The reduction in intraoperative blood loss in patients receiving spinal nerve block, which was reported in the retrospective study from the same unit [11], was confirmed in the present study. This reduction in blood loss appeared to lead to a reduced requirement for blood transfusion. Thirty-one percent of patients who received conventional general anaesthesia in the retrospective study required blood transfusion, compared with none who received spinal nerve block ($P < 0.001$). The corresponding values in the prospective study were 22% and 11%; this difference, however, is not statistically significant. The mean incidence of blood transfusion in the present study (16.3%) was lower than that in recent studies which have demonstrated an adverse effect on long-term survival of patients who received blood transfusion associated with surgery for colonic or rectal carcinoma [5–7]. In these studies, 45–65% of patients required blood transfusion. Blood loss and blood transfusion are known to increase the risk of anastomotic disruption after colonic surgery [4]; more recent observations in respect of long-term survival appear to be related to recurrence or spread of tumour, and may be associated with an immunological mechanism similar to that which has been proposed in the improved survival of a transplanted kidney in patients who have received blood transfusion [17].

The two groups were similar in respect of other factors which might have influenced blood loss, such as type of operation and duration of surgery; in addition, all operations were elective, and all but three were performed by the same surgeon. Spinal nerve block may merit consideration for colonic surgery solely because of its effect on reducing blood loss. However, much of this reduction was probably the result of profound hypotension, a physiological state which is not without risk for patients in this age group [18].

In this study, spinal nerve block offered no advantage in terms of the incidence of, or mortality from, anastomotic breakdown. However a reduction in, or total abolition of, blood transfusion is desirable in patients undergoing surgery for colorectal cancer [17, 19] and high spinal nerve block produces a significant reduction in blood loss and reduces the requirement for donor blood.

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COMPARISON OF TWO METHODS OF AXILLARY BRACHIAL PLEXUS ANAESTHESIA

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SUMMARY

Comparison of the trans-arterial and Winnie techniques of axillary brachial plexus block was made in two groups of patients. This study did not find any statistical difference between the two techniques.

Axillary brachial plexus block is a simple method of anaesthetizing the arm. It carries no risk of pneumothorax. Commonly used by anaesthetists who perform brachial plexus blocks occasionally, its success depends on the placement of the tip of the needle inside the axillary sheath. However, this is not always easy to achieve. The trans-arterial approach offers a definitive end-point for the position of the needle. This technique is described in several textbooks [1,2] and widely practised, but its results have never been evaluated in the literature. It was proposed to compare the trans-arterial approach with the more established technique advocated by Winnie [3].

PATIENTS AND METHODS

Sixty patients older than 18 yr undergoing upper limb surgery were studied. Approval for the study was given by the local ethics committee and informed consent was obtained from each patient before entering the trial. The patients were allocated randomly to one of two groups. Brachial plexus blocks were performed using either the trans-arterial (group A) or the Winnie (group B) approaches. All patients were premedicated with temazepam 10–20 mg and metoclopramide 10 mg. On arrival of the patient in the operating theatre an indwelling cannula was placed in a vein in the arm not requiring surgery. The other arm was abducted to about 90°, with the hand resting on a pillow next to the patient's head. The axillary artery was identified as far proximally as possible. For both blocks, an extension set primed with local anaesthetic was connected to the needle.

Group A

The index and middle fingers of one hand were pressed over the artery as near to the anterior axillary fold as possible and a 23-S.W. gauge needle inserted between them into the artery. Aspiration was performed by an assistant continuously as the needle passed through the artery and once aspiration of blood no longer occurred, the solution was injected. After completion of the injection, the needle was quickly withdrawn and the arm was brought down to the patient's side while maintaining firm digital pressure over the puncture site for 5 min to prevent haematoma.

Group B

The index finger was placed over the artery and a 22-gauge B & D regional block needle was inserted immediately above the finger at an angle of 20° to the skin. It was directed parallel and just next to the artery. The needle was advanced slowly until a snap was felt as the needle penetrated the sheath or paraesthesiae were obtained. The syringe was aspirated and if no blood was obtained the solution was injected slowly. As soon as the injection was completed, the needle was withdrawn and the arm was brought down. Firm digital pressure was directly applied behind the needle during and immediately after the injection, to encourage cephalad spread of local anaesthetic. If blood was aspirated, the patient was excluded from the trial.

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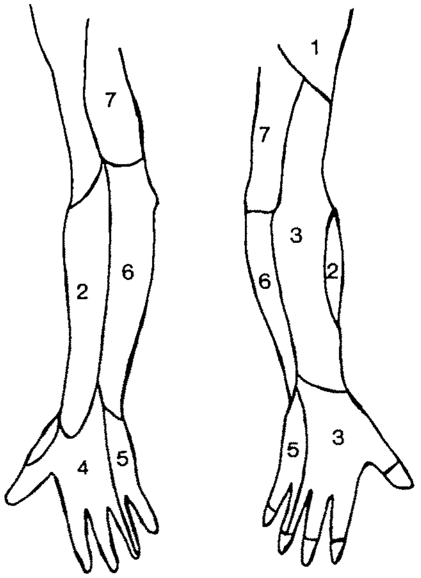

FIG. 1. Cutaneous innervation of the upper limb. 1 = Axillary nerve; 2 = musculocutaneous nerve; 3 = radial nerve; 4 = median nerve; 5 = ulnar nerve; 6 = medial cutaneous nerve of forearm; 7 = medial cutaneous nerve of arm.

In both groups 1% prilocaine solution 40 ml was injected slowly over 2 min with repeated aspiration to detect and avoid intravascular injection.

All blocks were performed randomly by the authors and then assessed by one of two independent observers, who did not know which technique was used. The sensory changes were assessed 40 min after the injection. Sensory loss was assessed with a 25-S.W. gauge needle using a scale 0–2 (0 = no sensory loss; 1 = loss of pinprick; 2 = loss of touch). Sensory testing was carried out in the areas supplied by the following nerves: axillary, musculocutaneous, radial, median, ulnar, medial cutaneous nerve of forearm and medial cutaneous nerve of arm (fig. 1). For the sake of simplicity, sensory blockade grades 1 and 2 have been combined together. We used definitions described by Vester-Andersen and colleagues [4,5]: a failed block was one where the sensory blockade involved only a single or none of the following nerves: median, ulnar, radial or musculocutaneous. Successful blocks were classified as either complete (loss of sensation in areas supplied by all cutaneous nerves peripheral to the axillary nerve), or incomplete.

Two patients were excluded from the trial: one from group A as a result of difficulty in penetrating the artery and the other, from group B, because of accidental puncture of the artery.

Student's *t* test was used to compare the mean age, weight and height of the patients and Fisher's exact probability test was used to compare both the failure rate and the frequency of blocked nerves in all patients.

RESULTS

The mean ages, weights and heights of the 29 remaining patients in the two groups were comparable (table I).

The results of axillary brachial plexus anaesthesia in each group are given in table II. The level of incomplete block (31%) was comparable to that of other reported series [4]. Six patients in group A had a failed block, but only three in group B. The difference was not statistically significant.

TABLE I. *Characteristics of patients (mean ± SEM)*

	Age (yr)	Weight (kg)	Height (cm)
Group A (n = 29)	42.8 ± 4.1	68.9 ± 2.0	163.0 ± 1.6
Group B (n = 29)	43.1 ± 2.7	64.9 ± 1.7	167.0 ± 1.7

TABLE II. *Results of axillary brachial plexus anaesthesia*

	Group A (n = 29)	Group B (n = 29)
Complete block	14 (48%)	17 (59%)
Incomplete block	9 (31%)	9 (31%)
Total failure rate	6 (21%)	3 (10%)

TABLE III. *Frequency of blockade of each cutaneous nerve*

	Group A (n = 29)		Group B (n = 29)	
Nerve	No.	%	No.	%
Axillary	23	79.3	16	55.2
Musculocutaneous	17	58.6	21	72.4
Radial	23	79.3	21	72.4
Median	17	58.6	24	82.7
Ulnar	21	72.4	23	79.3
Medial cutaneous, forearm	22	75.9	25	86.2
Medial cutaneous, arm	20	70.0	25	86.2

General or additional local anaesthesia required before surgery

	Group A ($n = 29$)	Group B ($n = 29$)
neral anaesthesia	8	6
rve block	2	3
cal infiltration	4	0

III shows frequencies of the blockade of al nerves following the two approaches. erence did not reach statistical signifi-

up A (table IV), eight patients received a anaesthetic: six for a failed block and use of extreme anxiety. In addition, six local infiltration for a peripheral nerve group B six patients received a general tic; three for a failed block and three for ete block. In addition three patients a peripheral nerve block.

DISCUSSION

tudy we did not demonstrate any obvious e of one technique over the other. The ate of 90 % in group B was similar to the 4 % success) for the Winnie approach to ary brachial plexus block described by nvestigators [5–7].

gh there was no significant difference the two techniques, the failure rate was high in group A as in group B. The lower rate in group A (79 %) was surprising, as point for injection is clearly defined. We assume that the needle was inserted too nce it had passed through the artery. A and is needed to control accurately the nt of the needle as it passes through the We have found this easiest to achieve with the arm manipulating the needle n a firm surface. Mastery of any particular e of brachial plexus block is related to practice. Hudon and Jacques [8] reported ase in their success rate in the later part of of 165 blocks, compared with the g.

common occurrence to find unblocked with axillary brachial plexus anaesthesia this respect our results from both groups t unusual. De Jong [9] and Lanz, Theiss and Jankovic [10] found the musculocutaneous, axillary and radial nerves were most likely to remain unblocked. In this study, it was found that the axillary nerve was more frequently blocked in group A (79.3 %) than in group B (55.2 %) ($P = 0.08$). This is probably explained by the fact that the axillary nerve is situated deep to the artery, where local anaesthetic agents are deposited in the trans-arterial approach. A lower frequency of median nerve blockade was recorded in group A (58.6 %) than in group B (82.7 %). Although this was not statistically significant ($P = 0.07$) it may have caused clinical problems requiring conversion to general anaesthesia. To improve the chances of blocking the median nerve, one could withdraw the needle to lie just superficial to the axillary artery and deposit some local anaesthetic there. Whatever technique is used, unblocked nerves will require either additional local infiltration or peripheral nerve block.

All brachial plexus blocks have potential complications. For the axillary approach, haematoma formation [11], vascular spasm [12] and inadvertent intravascular injection [13] have all been reported previously. Although none of these problems occurred in our study, it is obvious that the trans-arterial technique carries a higher theoretical risk of vascular complications. We attempted to minimize haematoma formation by maintaining firm pressure for at least 5 min after the withdrawal of the needle. We also used an immobile needle technique [14] in an attempt to reduce the risk of intravascular injection. This allowed the anaesthetist to immobilize the needle while the assistant manipulated the syringe. Injection was slow, with repeated aspiration to detect minor needle displacement. We conversed with the patient during the injection in order to detect early CNS toxicity.

Winnie [14] advocate that, when his technique is used, correct positioning of the needle inside the axillary sheath should be determined by seeking paraesthesia or a snap as the needle penetrates the axillary sheath. A problem may arise when neither occur (one patient in group B). Searching for paraesthesia may increase the risk of nerve damage [15], although this has been contested in a recent review [16]. Paraesthesia is also unpleasant for the patient and difficult to elicit in heavily premedicated patients. A snap was felt in 72 % of patients in group B. Of the remainder, paraesthesia was encountered accidently in two and searched for and found in five.

The use of a short bevel needle makes the snap more easy to feel and should decrease the risk of nerve damage [17].

In conclusion, the trans-arterial approach to brachial plexus anaesthesia with its definitive end-point, is an easy and safe technique. It can also be self taught. However, haematoma, vascular insufficiency and inadvertent intravascular injection are all potential complications. We feel that a larger series is needed to evaluate its relative merits before an attempt is made to encourage its wider use.

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POSTOPERATIVE ANALGESIA BY CONTINUOUS EXTRADURAL INFUSION OF BUPIVACAINE AND DIAMORPHINE

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SUMMARY

Three solutions administered by continuous extradural infusion for postoperative analgesia were compared in a randomized, double-blind manner. All patients underwent major abdominal gynaecological surgery and received 0.125% bupivacaine in 0.9% saline/diamorphine in 0.9% saline (0.5 mg in 15 ml) or diamorphine mixed with 0.125% bupivacaine (0.5 mg in 15 ml), at a rate of 15 ml h^{-1}. The bupivacaine–diamorphine mixture provided significantly superior analgesia compared with either bupivacaine or diamorphine alone. No major side effects were encountered.

Prevention of postoperative pain can be achieved more efficaciously by the use of continuous infusion techniques than by the intermittent injection of analgesic drugs which are invariably given after pain has developed. Postoperative analgesia provided by the extradural infusion of local anaesthetic or opioid drugs has been described after abdominal, thoracic and orthopaedic surgery [1–4]. It is clear that these methods can be effective, but as yet there has been little published work comparing various extradural infusion regimens in a controlled fashion [5].

In this study, we have compared three extradural infusion regimens in a randomized, double-blind manner, and examined analgesic efficacy, side effects and the safety of the technique. The solutions used contained either bupivacaine or diamorphine alone, or a mixture of the two.

PATIENTS AND METHODS

Sixty patients (aged 18–70 yr, ASA I or II), undergoing major abdominal gynaecological surgery were admitted to the study, which was approved by the local Ethics Committee.

Before operation and after receiving a full explanation, the patients completed a series of visual analogue scales and a symptom checklist, identical to those used in the postoperative assessments.

The patients received diamorphine 5 mg and atropine 0.6 mg i.m. 1 h before arrival in the anaesthetic room, where an i.v. infusion of Hartmann's solution was commenced. An extradural catheter was inserted at the T10–11 or T11–12 space and 2% plain lignocaine solution 20 ml was administered. General anaesthesia was induced using thiopentone and maintained with nitrous oxide, plus 0.5% halothane or 1% enflurane in oxygen, using a facemask with the patient breathing spontaneously. Bupivacaine 0.5% plain solution 10 ml was given extradurally at 1 h or during wound closure, whichever occurred first.

A continuous extradural infusion was commenced at the end of surgery using solutions prepared by the hospital pharmacy. No clinician was aware of the contents of the infusions and patients were allocated randomly to three groups: group 1 received 0.125% bupivacaine 18.75 mg at 15 ml h^{-1}; group 2 received diamorphine 0.5 mg h^{-1} in 0.9% saline 15 ml; group 3 received diamorphine 0.5 mg h^{-1} in 0.125% bupivacaine 15 ml. The solutions were administered using an Imed cartridge system or a Watson–Marlow roller pump. A 30-ml paediatric burette was inserted in

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the tube leading from the infusion bag to check the amount infused every hour. It was replenished every 2 h by the nursing staff.

It was explained clearly that, if postoperative pain relief proved to be inadequate, further medication would be provided on request (with i.m. diamorphine), and the patient would be withdrawn from the study.

The extradural site, duration of operation, blood loss and type of incision (transverse or midline) were recorded.

On recovery, the upper limit of analgesia to pinprick was determined and motor blockade of the lower limbs was assessed on a five-point scale: 0 = full power; 1 = weak but able to raise limbs against gravity; 2 = good movement, gravity compensated; 3 = minimal movement; 4 = paralysis.

Assessments were made at 2, 4, 6, 12 and 21 h following completion of the operation, or at the time the patient requested further analgesia. At each assessment, the patient completed a symptom checklist and a series of visual analogue scales with the limits described as follows: no pain—the worst pain imaginable; alert—drowsy; steady—dizzy; muzzy—clearheaded; clumsy—well co-ordinated; very well—very ill. An observer assessment of overall efficacy was made by the attending anaesthetist (D.S., A.L., or both) using a visual analogue scale (extremely poor—extremely good), and the upper level of analgesia to pinprick and the degree of motor blockade were recorded.

The nursing staff measured heart rate, arterial pressure, rate of ventilation and volume of extradural solution infused, at 1-h intervals.

Comparisons were made between groups using Kruskal–Wallis and Mann–Whitney tests. Comparisons of the extent of analgesia within groups were made using Mann–Whitney tests, and numbers of patients requesting further analgesia were compared using a χ^2 test.

RESULTS

The groups were comparable in age, height, weight, extradural site, type of incision, duration of operation and blood loss (table I).

Analgesia and motor blockade were assessed on recovery from anaesthesia and there were no significant differences between the groups (table II).

TABLE I. *Details of patients (mean ± SD)*

	Bupivacaine	Diamorphine	Mixture
Age (yr)	43 ± 12	38 ± 11	41 ± 9
Height (cm)	162 ± 6	162 ± 6	162 ± 7
Weight (kg)	65 ± 12	64 ± 9	66 ± 12
Extradural site			
T10–11	15	14	16
T11–12	5	6	4
Incision			
Transverse	15	14	13
Midline	5	6	7
Duration of operation (min)	95 ± 27	87 ± 25	82 ± 20
Blood loss (ml)	283 ± 180	217 ± 169	244 ± 171

TABLE II. *Analgesic levels to pinprick and degree of motor blockade immediately after operation*

	Bupivacaine	Diamorphine	Mixture
Analgesic level			
Median	T4	T4	T4
Range	T3–T7	T3–T5	T3–T6
Mean ± SD	T4.1 ± 1.1	T4.1 ± 0.6	T4.1 ± 1.0
Motor blockade			
0	4	2	0
1	2	5	7
2	3	5	5
3	6	5	5
4	5	3	3

One patient in each group was withdrawn between 12 and 21 h because of dislodgement of the extradural catheter. All other patients were withdrawn from the study because analgesia was requested in addition to that provided by the extradural infusion; there was a significant difference between the groups at the end of the study ($P < 0.05$) (fig. 1).

Comparison of the three groups demonstrated a highly significant difference in VAS for postoperative analgesia at each assessment ($P < 0.01$). Figure 2 shows the scores at each time point. Scores made by patients at the time of withdrawal were used at each subsequent time interval for statistical comparison between groups to avoid selecting out only those patients with adequate analgesia. The bupivacaine–diamorphine mixture (group 3) invariably provided superior analgesia to that from either bupivacaine (group 1) or diamorphine (group 2) alone. There were no significant differences between groups 1 and 2 at any time.

In addition to pain assessment, a further series of VAS was used to assess general well-being

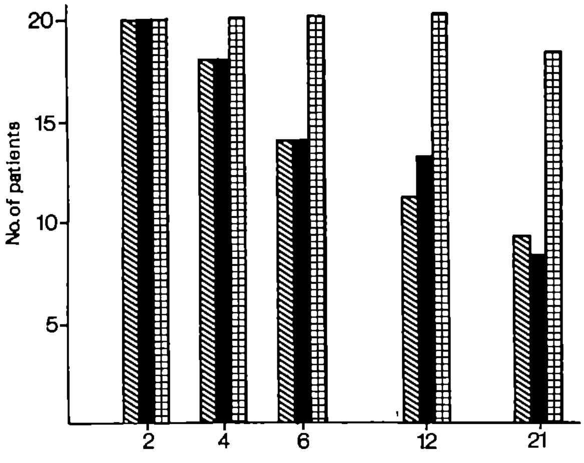

FIG. 1. Number of patients remaining in the study at each time period. Cross-hatched columns = bupivacaine group; black columns = diamorphine group; squared columns = mixture group.

during each time period. These variables fluctuated independently of pain scores and comparisons of these subjective feelings have been confined to those patients with an adequately functioning extradural infusion and good pain relief. At the 12- and 21-h assessments both the groups receiving diamorphine scored significantly higher on indices of sedation (alert—drowsy; muzzy—clearheaded), but both groups receiving bupivacaine scored significantly better than the diamorphine alone group on the general scale (very well—very ill) at 21 h.

There were significant differences in the observer VAS for analgesia between the groups at 4 h and 6 h; in each case the mixture was judged superior to either bupivacaine or diamorphine alone.

In all groups the upper analgesic level regressed during the first 4 h after operation. After this time the level of blockade was maintained well in most patients receiving bupivacaine either alone or as part of the mixture, but in some patients the block became completely unilateral, with no analgesia to pinprick on one side of the body. This occurred in four patients in group 1 and six in group 3. The upper levels of blockade of those remaining in the study at each time point are illustrated in figure 3. There were no significant differences in level of blockade between groups 1 and 3 at any time. Four patients in group 2 still had an analgesic level to pinprick at 21 h.

In the majority of patients, motor blockade in

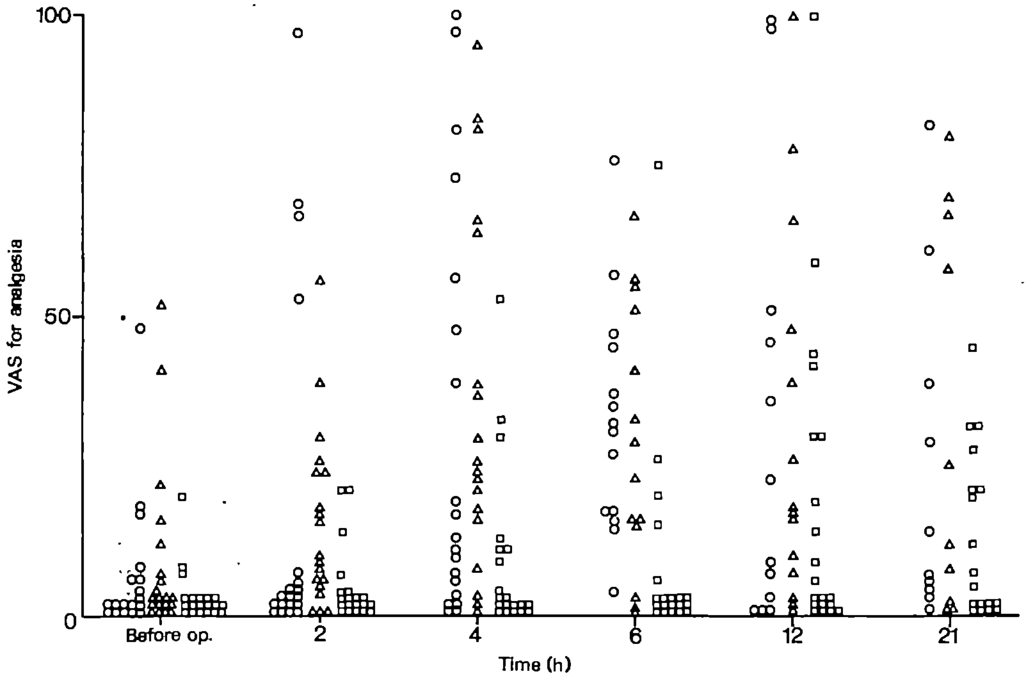

FIG. 2. Visual analogue scores for analgesia at each time point. ○ = Bupivacaine group; △ = diamorphine group; □ = mixture group.

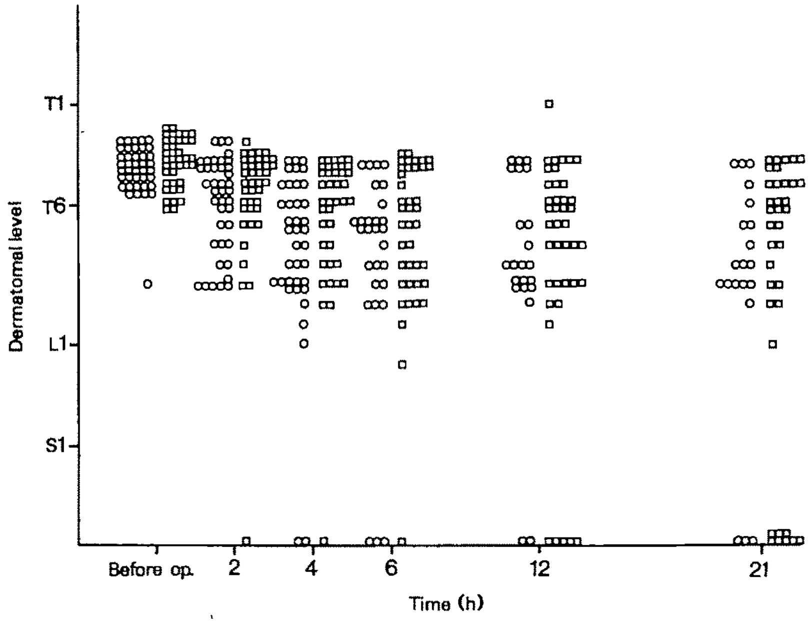

FIG. 3. Individual levels of blockade in patients receiving bupivacaine. Analgesic levels on each side of the body are represented separately, giving two values for each patient. ○ = Bupivacaine group; □ = mixture group.

TABLE III. *Degree of motor blockade at 21 h. In those patients with differing degrees of blockade in right and left legs, the most profound degree of blockade is recorded*

Degree of motor blockade	Bupivacaine	Diamorphine	Mixture
0	5	11	14
1	3	0	4
2	1	0	0
3	1	0	0
4	0	0	0
Infusion stopped	10	9	2

TABLE IV. *Side effects. Patients affected in each group. Patients with a suprapubic catheter* in situ *were excluded from the analysis*

	Bupivacaine	Diamorphine	Mixture
Ventilatory depression (< 10 b.p.m.)	0	0	0
Hypotension requiring treatment	0	1	0
Urinary retention (No. catheterized/ No. studies)	9/19	8/16	13/18
Itchiness	2	9	16
Nausea or vomiting	12	10	9

the lower limbs regressed rapidly over the first 6 h. No patient in group 2 had any degree of motor blockade after 6 h. One patient in group 1 experienced an increase in motor blockade after initial regression and had grade 3 blockade at 21 h, but no other patient had a motor block greater than grade 2 at that time. The degree of blockade in all patients at 21 h is illustrated in table III.

Other side effects are listed in table IV.

There was no evidence of reduced rate of ventilation (< 10 b.p.m.) in any patient following commencement of the extradural infusion.

Only one patient (group 2) required treatment for hypotension. This patient received ephedrine 5 mg i.v. immediately after return to the ward and gave no further cause for concern.

Urinary retention requiring catheterization was common in all groups, slightly more so in the group receiving the mixture.

DISCUSSION

This study has demonstrated that postoperative analgesia provided by an extradural infusion of bupivacaine and diamorphine is superior to the analgesia provided by each drug alone. The technique had a high level of patient acceptability and there were no major side effects.

The superior analgesia provided by the mixture may result from the combined effects of afferent neural blockade, selective spinal analgesia and a central analgesic effect secondary to vascular absorption of diamorphine [6, 7]. The greater incidence of sedation in the groups receiving diamorphine was evidence of a central effect. Because opioids and local anaesthetics have different sites and modes of action, a combination should allow minimal amounts of each to be used with good effect, reducing the possibility of overdosage with either agent.

The addition of diamorphine to a bupivacaine solution had no significant effect on the level of sensory blockade and there was no difference in the incidence of unilateral blockade between the bupivacaine-containing groups. A striking difference between the two groups was the superior analgesia in those patients with unilateral blockade who received the mixture, compared with those who developed a unilateral block but were receiving bupivacaine alone. An analgesic level to pinprick was demonstrable at 21 h in four patients who received diamorphine alone. Segmental blockade by opioids has been demonstrated previously following the extradural administration of morphine 10 mg [8].

It has been suggested that administration of an opioid parenterally can maintain or enhance a regressing extradural block [9]. In our study block level was maintained well in both groups receiving bupivacaine, once the effect of the local anaesthetic bolus administered in the operating theatre had worn off. This generally took 4–6 h. After this time the level of blockade did not regress in either group, but some patients in both groups developed a completely unilateral block. The cephalad extent of analgesia to pinprick was maintained well in the blocked side of all those developing unilateral blockade. In our opinion it is inappropriate to use mean block levels when commenting on extradural infusions because inclusion of unilateral blocks may lead to the false implication that all extradural infusions demonstrate regressing blocks. This was not the case in our study.

Frequent direct questioning elicited a high incidence of minor complaints. Itchiness was common in those patients receiving extradural diamorphine, but treatment was requested by only one patient. This patient received the mixture and complete resolution of the itch followed the administration of naloxone 0.2 mg i.v., the analgesia being unaffected. Nausea and vomiting occurred with similar frequency in the three groups. Urinary retention requiring catheterization was a common side effect of similar incidence in all groups. This finding is in significant contrast to the widely differing incidences of urinary retention reported in similar circumstances in other studies [10–12].

The most important complication of extradural opioid administration is ventilatory depression. We used diamorphine in this study because it offered a reduced likelihood of late respiratory depression compared with morphine [8, 13]. Early respiratory depression [14] depends on bolus administration of diamorphine into the extradural space and does not occur with slow infusions.

Diamorphine undergoes deacetylation to monoacetyl morphine and morphine in body tissues and blood and its stability is important. It is soluble in 0.9% sodium chloride solutions [15, 16], and this is dependent on pH. Diamorphine has a pK of 7.6 at 23 °C [17] and is highly ionized in 0.9% saline (pH = 5.39) and the bupivacaine–diamorphine mixture (pH = 5.28). It is also stable in these solutions with regard to degradation to monoacetyl morphine and morphine [18], and can be given as an infusion. Diamorphine is more lipophilic than morphine, and has a more profound central effect after extradural administration because of more rapid systemic absorption and greater potency. Conversion to morphine in the extradural space would require diamorphine to be taken up by extradural tissue and deacetylated. It is not known if this local metabolism occurs, but a comparison of the pharmacokinetic profiles of hydrophilic or lipophilic opioids following i.m. or extradural administration suggests that significant extradural tissue uptake does not occur [19, 20]. Extradural tissue uptake would increase the volume of distribution of the drug within the extradural space and alter the pharmacokinetic profile, in that there would be a reduced rate of systemic absorption and lower peak plasma concentrations. Both the diamorphine-containing solutions have minimal buffering capacity and rapidly attain body pH. The pH of the solution is therefore unlikely to be a major factor altering systemic uptake or dural permeability of diamorphine. There is minimal conversion of diamorphine to morphine in the subarachnoid space [21], and the increased lipid solubility results in rapid cord penetration [6], which is important in limiting cephalad spread. For these reasons we believe diamorphine to be a suitable drug for extradural administration by a continuous infusion technique.

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CONTINUOUS EXTRADURAL INFUSION OF 0.125% BUPIVACAINE FOR PAIN RELIEF AFTER LOWER ABDOMINAL SURGERY

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SUMMARY

Twenty women, undergoing lower abdominal surgery, were allocated randomly to receive a continuous extradural infusion of either 0.125% bupivacaine or placebo at a rate of 15 ml h^{-1}*. All had received an intra-operative extradural block. Pain scores were recorded at 30, 60, 90, 120, 150, 180, 240 and 360 min after surgery. From 150 min onwards there was a significant benefit for those receiving the active drug. Six of nine patients in this group had adequate analgesia over the 6-h study period, while all patients in the placebo group required further pain relief.*

There is considerable interest in continuous extradural infusions of dilute local anaesthetic solutions for the relief of pain in labour, and success has been claimed for 0.125% bupivacaine given at a rate of 10 ml h^{-1} [1]. Postoperative pain probably requires more profound nerve block because analgesia after operation involves sensory somatic nerves [2]. When using continuous dilute infusions it is generally necessary to inject a more concentrated bolus initially, relying on the infusion to maintain the block rather than initiate it.

Although there is clinical evidence that these infusions are effective, we are not aware of a controlled study which unequivocally demonstrates this in postoperative pain. We have therefore compared the duration of analgesia following an initial bolus of 0.5% bupivacaine after which the extradural space was infused with either saline or 0.125% bupivacaine.

METHODS AND RESULTS

Twenty women undergoing major intra-abdominal gynaecological surgery were studied. The investigation was approved by the regional Ethics Committee and consent was obtained from all patients.

Premedication comprised diamorphine 5 mg and atropine 0.6 mg given i.m. approximately 1 h before induction of anaesthesia.

A single end-hole extradural catheter (Portex) was inserted at the T11–12 space, for approximately 3 cm into the extradural space. Two percent plain lignocaine 16–20 ml was injected slowly over 2 min, while verbal contact was maintained with the patient. Light general anaesthesia was induced subsequently with thiopentone 400–500 mg and maintained with 66% nitrous oxide in oxygen and 0.5–0.8% enflurane given by facemask. Surgery then proceeded.

All patients received an extradural "top-up" of 0.5% bupivacaine 10 ml 1 h after the injection of lignocaine, or on peritoneal closure, whichever was earlier.

The patients were allocated randomly to two groups. Group 1 received an extradural infusion of 0.125% bupivacaine in saline at a rate of 15 ml h^{-1}. Group 2 received an extradural infusion of 0.9% saline at a rate of 15 ml h^{-1}. The infusion containers were marked identically in both groups. In all patients the infusion was commenced within 30 min of the intra-operative dose of 0.5% bupivacaine.

Solutions were delivered by either an Imed 902 volumetric pump or a Watson–Marlow 101UA peristaltic pump. In all cases a 30-ml graduated burette was interposed between the infusion

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container and the pump, to permit hourly confirmation of delivered volumes.

Sixteen patients were given ephedrine 30 mg i.m. at the end of surgery as prophylaxis against postoperative hypotension. An independent observer (ML) visited the patients at 30, 60, 90, 120, 150, 180, 240 and 360 min after the end of surgery. The degree of postoperative pain was assessed using a visual analogue scale (VAS) of 100 mm with extremes "no pain" and "worst pain imaginable". If a patient demanded further analgesia, an extradural "top-up" of 0.5% bupivacaine 6–8 ml was given and the study terminated. All patients were subsequently given an infusion of 0.125% bupivacaine until the next morning, according to our usual practice.

Difference between distributions were analysed by repeated measurements and paired analysis using the Wilcoxon two-sample test and Mann–Whitney test. Differences between frequencies were analysed by the Fisher exact one-sided test.

There were no significant differences in age, weight or height between the two groups. The mean duration of the surgical procedure was 58 min in group 1 (range 30–115 min) and 69 min in group 2 (range 33–120 min) ($P > 0.05$).

One patient in group 1 was withdrawn from the study because of a unilateral block. One patient in group 1 was given diamorphine 5 mg i.m. 5.5 h after surgery and the pain scores for this patient at 6 h were therefore excluded from analysis. Three patients in group 1 and all 10 patients in group 2 required an extradural top-up during the 6-h study period. This difference is significant ($P < 0.01$).

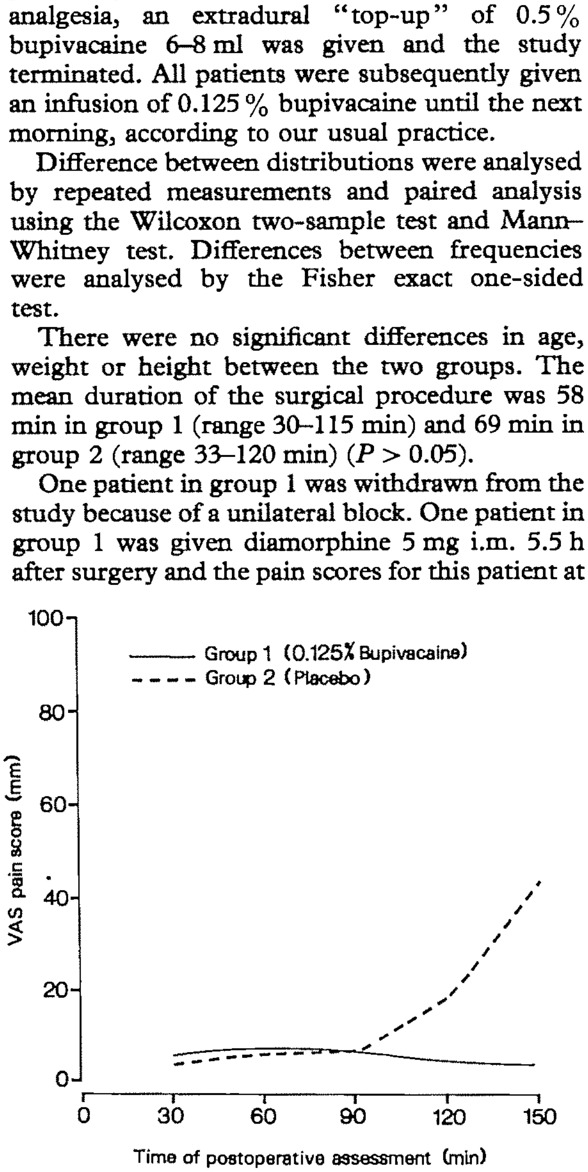

FIG. 1. Mean VAS scores of the two groups up to 150 min after operation.

All 19 patients had good analgesia in the early postoperative period and there was no significant difference between median VAS scores until 150 min (fig. 1). In all patients good pain relief was obtained from the "escape" bolus dose of bupivacaine.

COMMENT

The purpose of continuous infusions of local anaesthetic into the extradural space is to maintain a degree of nerve blockade compatible with analgesia. To achieve this, there should be a balance between the concentration and volume of the infused drug. Small volumes of high concentrations may be ineffective because of inadequate spread. Larger volumes of high concentration may be effective, but are likely to be accompanied by an unacceptable degree of motor block and the possibility of systemic toxicity. Trial and error over several years have suggested that 0.125% bupivacaine at a rate of 10–20 ml h^{-1} is an acceptable compromise for postoperative analgesia in lower abdominal surgery.

The present study shows that the extradural block produced by a bolus injection of 0.5% bupivacaine can be prolonged by infusing 0.125% bupivacaine at a rate of 15 ml h^{-1}. However, some patients require "top-up" doses from time to time. Once the necessary degree of nerve blockade has been "lost", it is necessary to give a bolus dose of a higher concentration of bupivacaine to re-establish the block. Bupivacaine 0.125% given as a single bolus often fails to produce a demonstrable nerve block and it may even fail to relieve labour pain unless it is repeated soon after the initial injection [3].

Lund and colleagues [4] found that continuous extradural infusions of bupivacaine failed to stop regression of an established block over 24 h, but they were able to re-establish the block with i.v. morphine. Other studies [5,6] have shown that the addition of an opioid to the local anaesthetic infusion increases analgesic effectiveness and prevents regression. Obviously, an extradural block does not treat discomfort originating outside the area of blockade, for example visceral or diaphragmatic pain. We have found that small i.m. doses of opioid are often required to deal with such discomfort in patients receiving only local anaesthetic in the extradural infusion. In the present study, no injections of opioid were given during the study period.

Continuous extradural infusion of bupivacaine 15 ml h^{-1} is an effective method of prolonging a block produced by a single bolus dose of 0.5% bupivacaine. However, it is not always adequate as the sole method of providing analgesia after lower abdominal surgery, and it may be necessary to give additional extradural bolus doses of 0.5% bupivacaine while increasing the rate of infusion, add small amounts of opioid to the solution or give parenteral opioids.

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ANAESTHESIA AND ACUTE DERMATOMYOSITIS/ POLYMYOSITIS

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SUMMARY

The anaesthetic management of two patients with severe muscle weakness—one suffering from acute dermatomyositis, the other from acute polymyositis—is described. Both patients presented for surgery for malignancy. Anaesthesia was induced with etomidate in one, thiopentone in the other. Alfentanil was used for analgesia and atracurium for muscle paralysis in both. Neuromuscular blockade was monitored using a peripheral nerve stimulator and no problems were experienced. Recovery of neuromuscular transmission and ventilatory function after operation were normal.

Dermatomyositis, a condition of unknown aetiology characterized by dermatitis, oedema and inflammation of muscle, is deemed to be a clinical variant of the same pathological process as that producing polymyositis [1,2]. Many patients date the onset of their condition from an infection, and in 20% of cases there is an associated neoplasm [3,4]. Dermatomyositis/polymyositis associated with neoplasia is normally acute in onset and is said to be reversible with successful treatment of the neoplasm. Clinically, the condition has the characteristics of a connective tissue disorder and may have features in common with other diseases of this group such as involvement of the joints. In dermatomyositis there may be facial rashes and erythematous cutaneous changes similar to those seen in scleroderma.

The onset of the condition may be acute or insidious. The principal feature is muscle weakness, which may be generalized, but it most commonly presents with bilateral involvement of the pelvic, shoulder and neck muscles. The onset of weakness may be preceded by prodromal symptoms of muscle aches, fever, joint pains and, in dermatomyositis, facial oedema. Involvement of other muscle groups can produce diplopia, dysphagia, ventilatory impairment and facial weakness. Heart failure may occur as a result of myocardial involvement. Death is usually caused by ventilatory failure, heart failure or a complicating infection. Treatment is with corticosteroids.

The problems that dermatomyositis/polymyositis are said to present for the anaesthetist are outlined in the standard textbooks as muscle weakness resulting in ventilatory insufficiency, myocardial involvement and dysphagia with the potential for soiling of the ventilatory tract [5,6]. However, the basis for these statements appears to be largely surmise, since there are only three published case reports of anaesthesia in acute polymyositis. These were all in the Japanese literature and two were published after the above statements were made [7–9].

The anaesthetic management is reported of two patients, one with acute dermatomyositis associated with a neoplasm of his gastrointestinal tract, the other with acute polymyositis and a neoplasm of the epiglottis. Both had severe muscle weakness and presented for resection of their malignancies.

CASE REPORTS

Patient No. 1

A 70-yr-old male (weight 80 kg) gave a 3-month history of weakness of the shoulder and thigh muscles. The onset was apparently sudden, but had been preceded for several days by aching of both muscle groups, and during the ensuing 3

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TABLE I. *Serum enzyme concentrations*

	Concentration (unit litre^{-1}) Patient 1	Concentration (unit litre^{-1}) Patient 2	Normal range (unit litre^{-1})
Creatine kinase	2590	4102	33–194
Hydroxybutyrate dehydrogenase	446	513	85–190
Aldolase	20	—	< 7.6
Alkaline phosphatase	599	—	35–130
Alanine amino transferase	159	116	7–45
γ-Glutamyl transferase	424	—	0–65

months the weakness had become worse. By the time he presented for surgery he was unable to rise from the sitting position or to elevate his arms above shoulder level.

He was a type II diabetic controlled on diet and for the previous 6 months had been treated for hypertension with nifedipine and frusemide. On admission his arterial pressure was 160/90 mm Hg. There was nothing else of note in his medical history.

Investigations

Serum concentrations of hydroxybutyrate dehydrogenase, aldolase, alkaline phosphatase, alanine amino transferase, and glutamyl transferase were increased (table I). Measurement of quadriceps strength [10] showed his maximum voluntary contraction strength to be 35.3 % of that expected for his body weight. Vital capacity (VC) was 3.2 litre (predicted 3.95 litre) and the ratio of forced expiratory volume in 1 s (FEV_1) to VC was 82 %.

Chest x-ray was normal, although on CT scan there was a suggestion of an opacity, "possibly a metastasis" in the posterior basal segment of the right lung. ECG showed some evidence of an old posterior myocardial infarction. Full blood count, glucose tolerance test and blood-gas tensions were normal. Barium enema and colonoscopy revealed a stricture at the junction of the sigmoid and descending colon. He had had no symptoms from this and was scheduled to undergo sigmoid colectomy.

Anaesthesia

Diazepam 10 mg was given by mouth 2 h before anaesthesia was induced with alfentanil 0.5 mg and etomidate 16 mg. Atracurium 20 mg was given initially, then a further 10 mg because the 20 mg proved to be clinically inadequate. Ninety seconds after the second dose the trachea was intubated.

The lungs were ventilated with nitrous oxide and oxygen in a ratio of 2:1, and 0.6 % enflurane. The operation lasted 2 h 15 min. Increments of alfentanil 0.5 mg were given every 30 min (total dose 2.5 mg). Neuromuscular transmission was monitored using a peripheral nerve stimulator (750 Digital–Bard Biomedical). Three incremental doses of atracurium 10 mg were given during the course of the operation when neuromuscular function started to recover. Systolic arterial pressure had been 200 mm Hg on arrival in theatre and heart rate 100 beat min^{-1}. The arterial pressure settled to between 140 and 160 mm Hg systolic for the duration of the operation and heart rate to between 85 and 100 beat min^{-1}. No irregularities were noted on the ECG. Enflurane was discontinued 10 min before the end of the operation, spontaneous ventilation was established and residual neuromuscular blockade antagonized with neostigmine 2.5 mg (and glycopyrrolate 0.6 mg). There was a rapid return of full neuromuscular function as denoted by a vigorous sustained contraction in response to a supramaximal stimulus of 100 Hz and no evidence of "fade" in response to sequential stimuli at 2 Hz. Lung volumes were measured before extubation using a Wright respirometer. Tidal volume was 600–800 ml and vital capacity 1200 ml. Negative inspiratory pressure was 20 cm H_2O. The trachea was extubated and the patient transferred to the recovery ward where his cardiovascular and ventilatory state remained stable.

He developed a chest infection in the immediate postoperative period, but this responded to physiotherapy and ampicillin. By the 6th day after operation his muscle weakness had improved dramatically; he was able to stand from the sitting position and raise his arms above his head. He was discharged home 13 days after the operation. He died at home 5 months later from bronchopneumonia. A post-mortem was not carried out.

Patient No. 2

The patient was a 47-yr-old man weighing 85 kg who was admitted for the treatment of bronchopneumonia. Two weeks previously he had had an influenza-like illness, with aching muscles and a headache. This was followed by the progressive onset of muscle weakness and ventilatory symptoms over the week preceding admission. His pneumonia responded to antibiotics, but a clinical and radiological diagnosis of fibrosing alveolitis was made. The muscle weakness persisted and affected both arms and legs, but was worse in the upper limbs. Although he was able to lift his arms above his head he was unable to hold them there and was able to rise from a squatting position with extreme difficulty. He complained also of hoarseness, and on examination was found to have a carcinoma of the epiglottis.

Investigations

Chest x-ray showed evidence of fibrosing alveolitis; ECG was normal. Arterial Po_2 was 10.1 kPa, but blood-gas tensions were otherwise normal. Vital capacity was 3.25 (predicted 4.75) litre and FEV_1/FVC 72%. Serum concentrations of creatine kinase, hydroxybutyrate dehydrogenase and alanine amino transferase were increased (table I). Muscle biopsy was performed and a diagnosis of acute polymyositis was made.

Prednisolone 80 mg on alternate days was started, with some improvement in his muscle weakness. On examination before surgery his arterial pressure was 140/90 and heart rate 80 beat min^{-1}. Ventilatory rate was 20 b.p.m. and he was slightly short of breath at rest. He was scheduled to undergo partial laryngectomy.

Anaesthesia

Lorazepam 2 mg by mouth and glycopyrrolate 0.4 mg i.m. were given 1 h before operation. Anaesthesia was induced with thiopentone 350 mg and the patient breathed nitrous oxide, oxygen and isoflurane spontaneously until anaesthesia was deep enough to allow intubation of the trachea using a fibreoptic laryngoscope. A test dose of atracurium 12 mg was given, with insignificant clinical effect. A further 25 mg of atracurium was given, followed by an infusion at a rate of 0.36 mg kg^{-1} h^{-1}. Neuromuscular block was monitored as in the first patient. Isoflurane was discontinued and alfentanil 4 mg given over 10 min, followed by an infusion of 0.5 μg kg^{-1} h^{-1}. Artificial ventilation with nitrous oxide and oxygen in a 2:1 ratio and 0.6% enflurane was maintained throughout the procedure. During the course of the operation attempts were made to reduce the rate of the infusion of atracurium, but these were unsuccessful and two further doses of atracurium (10 mg and 15 mg) had to be given at different times to maintain satisfactory neuromuscular blockade. Arterial pressure was monitored using an indwelling cannula, and central venous pressure through a catheter inserted to the basilic vein. The cardiovascular system was stable over the course of the operation and no ECG abnormalities were observed.

Surgery lasted 4 h and both infusions were stopped 30 min before the end. Neuromuscular blockade was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.6 mg, and naloxone 0.2 mg was given to counteract mild ventilatory depression. Tidal volume on recovery was 800 ml and VC 2.5 litre. The trachea was extubated and the patient transferred to the intensive care unit at 16.00 h, breathing 25% oxygen. His Pa_{O_2} was 12.0 kPa and Pa_{CO_2} 5.1 kPa. At 23.00 h that evening he was still breathing 25% oxygen; Pa_{O_2} was 15.7 kPa and Pa_{CO_2} 4.9 kPa. Tidal volume at this stage was 800 ml and VC 3 litre. He remained stable and was discharged to the ward the following day, where his recovery continued uneventfully. He was discharged from hospital 12 days later, receiving prednisolone 70 mg daily. His muscle weakness had improved and on discharge he was able to rise from the squatting position and to hold his arm above his head, although subjectively he felt tired and weak.

DISCUSSION

In common with three previous case reports [7–9], none of the problems outlined in the standard textbooks [5,6] was experienced in the management of either of these two patients. In neither instance was there any clinical evidence of undue sensitivity to neuromuscular blocking drugs, ventilatory function appeared to recover in a normal fashion after surgery, and there was no evidence of myocardial dysfunction.

Feldman [11] stated that some improvement in the muscle weakness seen in polymyositis occurs with the administration of an anticholinesterase drug, but gave no supportive evidence. He also reported that two of a series of 10 patients with the condition showed evidence of a myasthenic response to decamethonium, but with no reference to published reports. The fact that the condition is sometimes associated with a malignancy, and that malignancy itself can be associated with defects in neuromuscular transmission, does mean that these patients could be particularly sensitive to neuromuscular blocking agents [5]. In both instances, a relatively small dose of atracurium was given initially and a further dose only when the original proved to have little effect. In view of the nature of the disease—an acute inflammation of muscle and the possibility of hyperkalaemia—it seemed wise not to give suxamethonium.

The disease in both patients was of recent onset. In the first it did not involve the pharyngeal muscles, so the question of pulmonary aspiration did not arise. The second patient presented with pneumonia in addition to his muscle weakness, but also proved to have carcinoma of his larynx. Polymyositis involving the pharyngeal muscles or local pathology of the laryngopharnyx could both potentially cause aspiration. This patient also had chronic chest disease, so any of these three conditions could have been the cause of his pneumonia.

One difficulty in these patients is to determine if ventilatory function is impaired by the muscle weakness. Although the first patient was not breathless at rest and had normal blood-gas tensions, an individual who is so weak that he cannot stand is incapable of stressing his respiratory system, so any assessment of, for example, exercise tolerance is impossible. The second patient was breathless at rest, but had chronic chest disease. The FEV_1/FVC ratio does give some indication of ventilatory power, and in both patients the ratio was normal. Tests such as maximum breathing capacity and peak expiratory flow rate may have provided more sensitive indices of ventilatory reserve, but these were not performed. After operation, ventilatory function in both cases appears to have recovered normally. No formal measurements were made in the first patient beyond the immediate postoperative period as there were no indications to do so, but lung volumes and inspiratory force at that stage were satisfactory and progress thereafter appeared to be normal. Lung volumes and blood-gas tensions in the second patient were measured later and these had improved.

The newer short acting neuromuscular blockers and analgesic agents have obvious advantages, with a wider margin for error over the traditional agents such as morphine or tubocurarine when anaesthetizing patients whose cardiorespiratory reserve is impaired or patients who may respond unpredictably to anaesthetic or analgesic drugs. They can also be given by continuous infusion, allowing control of analgesia and neuromuscular blockade at a lower dose than with repeat bolus administration [12]. No objective measurement was made, in either patient, of neuromuscular transmission, but it was monitored in the conventional fashion, observing the power of the contraction elicited in response to tetanic stimuli and the presence of fade in response to repeated stimuli. Neither patient appeared to be unduly sensitive to neuromuscular blocking drugs, and the doses of these drugs in the three subjects reported previously [7–9] were all within the normal range, so again there was no evidence of undue sensitivity.

In the three previous reports of anaesthesia for patients with dermatomyositis [7–9] extradural analgesia was used during operation and for postoperative pain relief. The patient reported by Kato, Aruga and Wakasugi [7] had severe muscle weakness and was unable to stand, but ventilatory function was normal. Anaesthesia was induced with a mixture of fentanyl and droperidol, suxamethonium was given to facilitate intubation of the trachea and pancuronium 6 mg was given in 1–2 mg increments for muscle paralysis. They recommended avoiding suxamethonium in the acute form of the disease, stated that long-acting myoneural blockers should be given in "small divided doses" and that it should be assumed that all patients have myocarditis. Their patient had no ventilatory problems in the postoperative period. The patient described by Kashimoto and colleagues [9] had pre-existing chronic chest disease with $FEV_1/FVC = 44\%$. They used a similar technique and, despite the pre-existing ventilatory impairment, no problems were experienced. Ogino's patient [8] was given thiopentone, pancuronium and extradural analgesia and, again, no immediate problems occurred. The patient died 3 months later from bronchopneumonia precipitated by the immunosuppression produced by chemotherapy. One of the subjects of the present report also died several months after the operation. In all likelihood this was coincidental, although it is not possible to rule out entirely any connection between his death and his dermatomyositis.

From the report of these two patients and the three previous ones it appears that, provided elementary routine precautions are taken, the severe muscle weakness seen in acute dermatomyositis/polymyositis in itself need present few problems for the anaesthetist. More reports would have to be published, however, before the many other potential problems associated with this condition that are outlined in the standard textbooks could be discounted.

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DECONTAMINATION OF HALOTHANE FROM ANAESTHETIC MACHINES ACHIEVED BY CONTINUOUS FLUSHING WITH OXYGEN

P. A. RITCHIE, M. A. CHESHIRE AND N. H. PEARCE

SUMMARY

The contamination of four types of anaesthetic machine with halothane was sequentially sampled by mass spectrometry while the machines were continuously flushed with oxygen 8 litre min^{-1} for up to 24 h. Contamination decreased in an exponential manner. Machines fitted with Selectatec vaporizer mounting systems and with the vaporizer removed showed contamination < 0.02 parts per million (p.p.m.) of halothane after 12 h flushing. Machines with cage-mounted vaporizers or with vaporizers left connected to the Selectatec block demonstrated persisting contamination. The Fluotec Mk.4 vaporizer showed an improvement on earlier designs in this respect. Background contamination concentrations of > 0.05 p.p.m. were measured in a patient-free recovery area of an operating theatre suite. Concentrations increased to 1 p.p.m. when patients were admitted following halothane anaesthesia. Decontamination of anaesthetic machines to concentrations of halothane below those detected as background contamination within recovery areas may allow such machines to be used safely to anaesthetize patients at risk from halothane.

Contamination of anaesthetic machines and breathing systems with volatile anaesthetic agents occurs because of the high absorbtion and adsorption of these agents in rubber and plastic [1–3]. Such contamination is thought not to be a problem for the majority of patients undergoing anaesthesia. There are, however, groups of patients who should not be exposed to the halogenated hydrocarbon halothane, for fear of provoking a potentially life-threatening reaction, because of either susceptibility to malignant hyperpyrexia, or a past history of halothane-associated hepatitis (either proven or suspected).

The provision of entirely halothane-free anaesthetic breathing systems is neither expensive nor difficult. Availability of a halothane-free anaesthetic machine necessarily incurs greater expense, particularly in view of the multiplicity of sites at which the machine may be required and the probable infrequency of its use. Such machines are frequently of outdated design and have low levels of sophistication.

This study used a mass spectrometer to determine the halothane contamination of four different models of anaesthetic machine. The effects of flushing the machines with oxygen for prolonged periods of time were investigated to show if the contamination with halothane could be reduced or eliminated. The effect of leaving the halothane vaporizers connected to the machine whilst flushing took place was additionally investigated to determine if this altered the degree of contamination.

Contamination by halothane eluting from the machines at the end of the flush period was compared with the contamination with halothane occurring within the recovery area of an operating theatre suite.

EQUIPMENT AND METHODS

Four different models of anaesthetic machine were investigated (Ohmeda Ltd): Boyle Mk.2000, Boyle International Mk.2, Boyle Mk.M (all fitted with Selectatec Series Manifold vaporizer mount-

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ing systems) and the MiniBoyle machine incorporating a cage-mount halothane vaporizer. The cage-mount system refers to the British Standard taper fittings that fix the vaporizer to the machine back bar such that it cannot be removed by the anaesthetist. All the machines tested had been in routine clinical use and, consequently, were already contaminated with halothane. In order to standardize their contamination as much as possible, and to simulate their use in recent halothane anaesthesia, 2% halothane vapour in oxygen 2 litre min^{-1} was flushed through each machine for 1 h before the investigation. All machines with Selectatec fittings were loaded with halothane from the same vaporizer, filled to a pre-determined level before each run. Two of the machines, the Boyle Mk.2000 and the Boyle Mk.M, were additionally tested with flushes of 4% halothane, although this was not entirely representative of expected clinically utilized halothane concentrations because the flush period was of 1 h duration.

All machines were then flushed continuously with hospital pipeline oxygen, at an indicated Rotameter flow rate of 8 litre min^{-1}, after connection to the mass spectrometer as described below. Flushing continued for up to 24 h, terminating when the mass spectrometer either detected < 0.01 parts per million (p.p.m.) of halothane or showed that the halothane concentration was no longer decreasing.

The Boyle Mk.M machine was additionally tested with either a Fluotec Mk. 3 halothane vaporizer (Cyprane Ltd) or Fluotec Mk.4 vaporizer left on the Selectatec block, but in the "off" position.

Halothane contamination within a standard theatre recovery area was analysed sequentially at 5-min intervals over a 24-h period. Sampling was achieved at a site that could form the inspired air of a patient nursed within such an area, whilst there were patients in adjacent bays who may have received halothane anaesthesia.

A "Petra" quadrupole mass spectrometer (V.G.Gas Analysis Ltd) was used for all halothane measurements. The mass spectrometer was calibrated using the built-in calibration programme. This provides a calculation for calibration volumes, prepared from liquid halothane, for injection into a closed calibration loop in the instrument. Five channels were programmed each at a different calibration value: 20 p.p.m., 10 p.p.m., 1 p.p.m., 0.1 p.p.m. and 0.01 p.p.m. These were individually calibrated, the background effect of instrument noise and carrier gas (hospital pipeline oxygen) having first been subtracted. Liquid halothane for calibration was used as supplied by the manufacturer (May & Baker Ltd) and no correction was used for the known thymol. At a measurement mass number of 100, this arrangement gave the ability to measure accurately halothane concentrations from 2500 p.p.m. to 0.005 p.p.m. with a reproducibility of ±10%.

Sequential sampling times were programmed into the machine, and the elapsed flush time was recorded continuously. Sampling was set at 1-min intervals for the first 15 min of flushing and then at 15-min intervals for up to 24 h. Data were stored on the integral computer disc for later analysis.

The five pre-calibrated channels were examined and those that were not saturated nor showing excessively low readings were averaged. This produced two or three data points for any one sample measurement and the averaged concentration could then be determined against elapsed flush time.

The eluting gas flow from the anaesthetic machine was sampled via a 6-mm o.d. Teflon tube connected in a T-tube arrangement with uncontaminated plastic tubing. Unsampled outflow gas was discharged into a scavenging system. A continuous 4-litre min^{-1} gas flow was withdrawn by the mass spectrometer for analysis and this was also discharged into a scavenging system.

Calibration of the mass spectrometer and choice of the m/z line (the mass of the ion divided

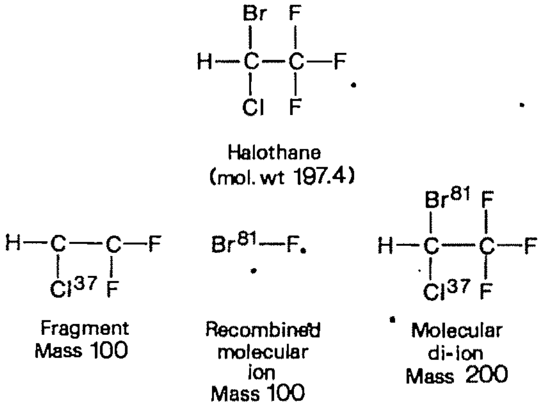

FIG. 1. Molecular structure and molecular weight (mol. wt) of halothane and the three most likely fragments detected by the mass spectrometer set at the 100 m/z line (the mass of the ion divided by its charge).

by its charge) for analysis are of crucial importance when accuracy and specificity of halothane identification are required. We investigated a number of *m/z* lines in the laboratory; an *m/z* line of 117 would have been the most sensitive in identifying halothane, but would not have differentiated between enflurane or isoflurane, which also generate fragments with identical mass numbers.

An *m/z* line of 129 would be specific for halothane, but it was discovered that hospital pipeline oxygen contains a variable concentration of the xenon isotope 129. Concentrations of approximately 0.2 p.p.m. could be identified. Because of the fractionation that occurs within the liquid oxygen storage tank, this concentration was unlikely to be constant. An *m/z* line of 100 gave the specificity required and was only marginally less sensitive than the other two. The *m/z* line of 100 is likely to correspond to any, or all, of the configurations shown in figure 1. The other likely volatile anaesthetic agents do not generate fragments at this *m/z* line, and studies on hospital

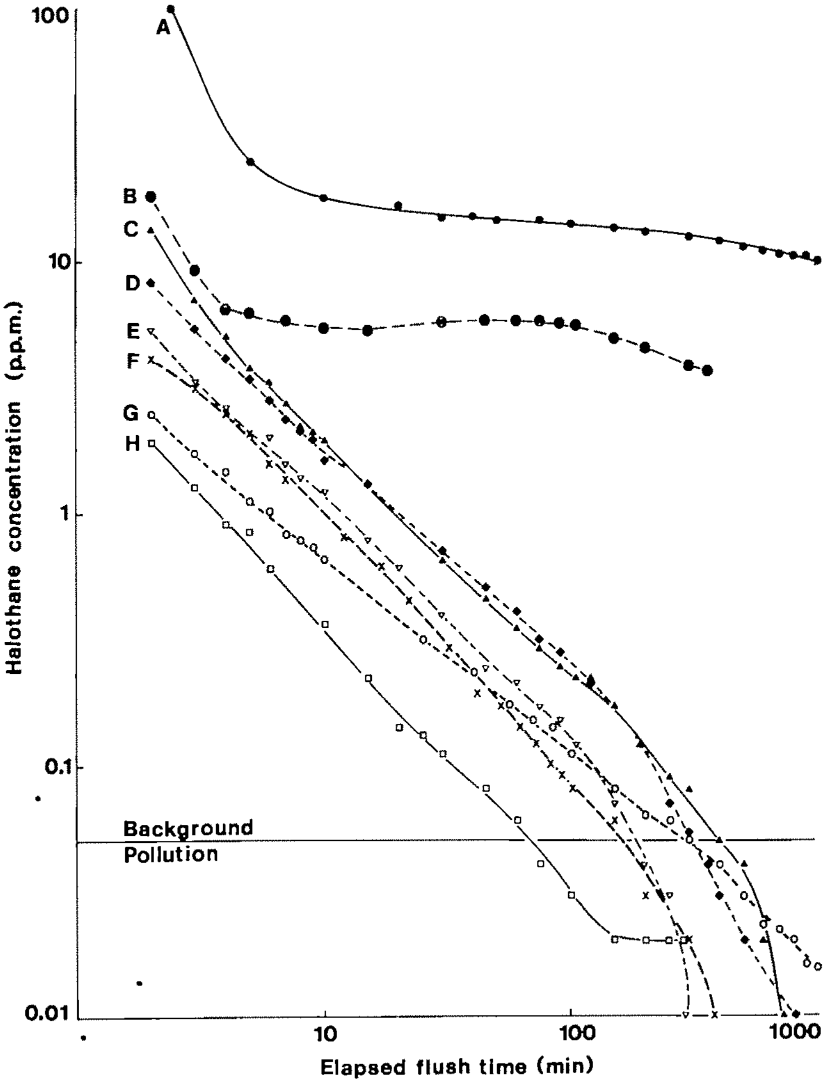

FIG. 2. Plot of eluting halothane concentrations from anaesthetic machines against time. A = MiniBoyle with cage-mount Fluotec Mk.3 *in situ*; B = Boyle Mk.M with Fluotec Mk.3 *in situ*; C = Boyle Mk.M loaded with 4% halothane; D = Boyle Mk.2000 loaded with 4% halothane; E = Boyle Mk.2000 loaded with 2% halothane; F = Boyle Mk.M loaded with 2% halothane; G = Boyle International Mk.2; H = Boyle Mk.M with Fluotec Mk.4 *in situ*.

pipeline oxygen revealed no significant contamination by such fragments. Hospital pipeline oxygen was thus used to provide a zero for the mass spectrometer.

Our five-point calibration procedure and two- or three-point measurement of each halothane sample at this m/z line gave specific and reproducible accuracy of halothane detection at the 0.01 p.p.m. level to within ±10%, and would identify the presence of halothane in concentrations lower than this.

RESULTS

The logarithmic halothane concentrations eluting from the machines are shown in figure 2, plotted against the logarithm of time.

The machines with Selectatec fittings (Boyle Mk.2000, Boyle International Mk.2 and Boyle Mk.M) all behaved similarly with respect to their washout characteristics. The Boyle Mk.2000 and Boyle Mk.M were almost indistinguishable, with 1 p.p.m. contamination at 10 min flushing, 0.1 p.p.m. at 100 min and 0.01 p.p.m. at 350–400 min (6 h). Concentrations of halothane detected by the mass spectrometer continued to decrease below this value, but accuracy of calibration would have been uncertain. The Boyle International Mk.2 showed a marginally slower rate of halothane washout.

A Fluotec Mk.3 vaporizer left in the locked "off" position, but still connected to the Selectatec mounting of the Boyle Mk.M, changed the washout characteristics of the machine: persisting contamination at 5 p.p.m. was detected. Connection of the Fluotec Mk.4 revealed a pattern of washout similar to that from the machine without the vaporizer, but halothane 0.02 p.p.m. elution persisted at the end of the run. This improvement upon the design of the Fluotec Mk.3 is caused by the fact that the inlet and outlet ports of the Fluotec Mk.4 engage with the spring loaded ports of the Selectatec block only when the vaporizer is switched on. Ports on the Fluotec Mk.3 are opened by mere connection of the vaporizer to the Selectatec bar.

The MiniBoyle machine with the cage-mounted halothane vaporizer *in situ* showed persisting contamination of halothane 10 p.p.m. and this could not be reduced despite 16 h continuous flushing.

The use of 4% halothane loading into the Boyle Mk.2000 and Boyle Mk.M machines showed the increased contamination of both machines as represented in figure 2. The machines, therefore, cannot be regarded as fully saturated when loaded with only 2% halothane, but rather this loading should be taken to reflect what is likely contamination occurring in clinical use.

Halothane concentrations of 0.05 p.p.m. were found in the theatre recovery area, even in the absence of patients. Concentrations increased to 1 p.p.m. when patients were admitted following halothane anaesthesia. In one such case it took 120 min for the halothane concentration to decrease to background, even though the patient was nursed in the area for only 80 min.

DISCUSSION

Our results show that, in anaesthetic machines contaminated with halothane, contamination is proportional to previous exposure to halothane. Machines with vaporizers removed from their Selectatec mountings demonstrated substantially reduced halothane contamination when subjected to continuous flushing with oxygen. Such contamination contained by the machines at the end of the flush period was well below the concentrations detected in our theatre recovery area. Why the Boyle International Mk.2 should have a slightly slower washout than the other two Selectatec fitted machines is not entirely clear. All machines had similar gas path lengths and methods of construction, including seals. Only one model from each range was tested and further work would be necessary to determine whether this finding is a consistent problem of the model or whether some individual variation in the machine was the likely cause. At such low levels of contamination it is probably of little significance, but it serves to demonstrate that the flush time should be greater than expected to allow for any such variation.

The dose of halothane necessary to trigger a reaction in a patient susceptible to malignant hyperpyrexia or halothane-associated hepatitis has not been established. No cases have been reported as having been caused by exposure of a patient to contamination with halothane occurring within a recovery area or operating theatre. One proven case of halothane hepatitis developed, in a susceptible patient, following anaesthesia with a contaminated machine and breathing system of American manufacture [4]. Subsequent investigation revealed halothane up to 200 p.p.m. in similar machines with vaporizers and breathing systems left connected.

Levels of halothane contamination occurring in the recovery area at our hospital are, we believe, representative of those likely to occur in other U.K. [5] and American [6] hospitals. The patient at risk will be exposed to at least halothane 1 p.p.m. if other patients, having received halothane anaesthesia, are nursed in the same area. Even when no other patient was present, the background contamination was 0.05 p.p.m. A true "halothane-free" anaesthetic for such patients would thus be almost impossible to administer if the patient is to be sent to the recovery area after operation.

In summary, we have demonstrated that it is possible, in the three models of anaesthetic machine tested, to decontaminate the machines and to achieve halothane concentrations well below those found in theatre/recovery environments. As no report has been published which demonstrates that a susceptible patient has suffered an untoward reaction when exposed to such low atmospheric pollutant concentrations, it may be theoretically possible to anaesthetize such patients with a decontaminated machine. Provided volatile alternatives to halothane are available, such a machine could be kept in routine clinical use within each theatre suite and, should inadvertent halothane contamination occur, the machine could be returned to its former status by flushing, by the method described, with either oxygen or medical air.

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Br. J. Anaesth. (1988), **60**, 864–867

CORRESPONDENCE

LOWER OESOPHAGEAL CONTRACTILITY AND SURGICAL STIMULATION

Sir,—Substantial differences in lower oesophageal contractility (LOC) in patients receiving standardized anaesthesia but undergoing different surgical procedures—abdominal hysterectomy and varicose vein surgery—have been demonstrated by Thomas and Aitkenhead [1]. In a recent study we have examined the effect of anaesthesia on LOC, but did not examine the effect of the surgical procedure [2]. We have re-examined the results and categorized them by surgical procedure as shown in table I and have used, for simplicity, the lower oesophageal contractility index (LOCI) to indicate the overall level of oesophageal activity. The LOCI has been described by Maccioli and colleagues [3] and is derived:

$$\text{LOCI} = [\text{SLOC rate (contractions min}^{-1}) \times 70] + \text{PLOC amplitude (mm Hg)}$$

TABLE I. *Mean values of lower oesophageal contractility index (LOCI) recorded during anaesthesia and grouped according to surgical procedure. The surgical procedures are ranked in order of the corresponding LOCI.* P *values derived from Student's* t *test: *0.06, †0.08, both compared with hernia repair*

Operation	Number	LOCI
Cholecystectomy	10	76*
Ovarian cystectomy	3	74
Vaginal hysterectomy	4	72
Abdominal hysterectomy	10	55†
Vaginal repair	2	49
Varicose veins	3	37
Hernia repair	11	29
Transurethral resection of prostate	1	24

In contrast to the study of Thomas and Aitkenhead, the anaesthetic dose we used was not constant, but changed cyclically over the range of 1.5–0.5 MAC. Despite this variation in anaesthetic dose, a trend in mean LOCI value was apparent: LOCI ranges from 76 during cholecystectomy to 29 during hernia repair (Student's *t* test: hernia *v.* cholecystectomy, $P = 0.08$; hernia *v.* abdominal hysterectomy, $P = 0.06$).

These results, together with those of Thomas and Aitkenhead, would suggest that LOC may provide a means for comparing levels of surgical stress or anaesthetic potency; additionally, further investigations involving the measurement of LOC will have to take account of the nature of the surgical procedure.

J. M. EVANS
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GASTRIC EMPTYING IN PREGNANCY

Sir,—I continue to be intrigued by the conflicting conclusions reached by various investigators relating to this topic. Recently, Simpson, Stakes and Miller [1] claimed that, even in early pregnancy, gastric emptying is delayed. Using the same technique (paracetamol absorption), Nimmo, Wilson and Prescott [2] found that gastric emptying was not delayed in labouring women who had not received opioid analgesia.

The techniques of measuring gastric emptying have been reviewed well by Nimmo [3] and by Morgan [4]. It appears that many of the methods offer information of doubtful validity. The specific attributes of pregnancy (patterns of gastrointestinal and hepatic blood flow, red cell mass and plasma volume; gastric hormones, and the like) could possibly make comparisons between pregnant and non-pregnant subjects inappropriate. The epigastric impedance technique [5] holds promise, but requires careful validation.

Surely the most reliable information would be obtained from a "direct" observation of the time taken for a test meal to disappear from within the gastric cavity. The Scintigraphic method would provide this, but would currently be unacceptable in the study of a pregnant woman. Similarly, a radiological technique may be contraindicated. May I remind your older readers, however, and inform the younger ones, of a study [6] which I reported in this Journal?

Twelve women in active labour were examined radiologically on one to three occasions, after taking a barium meal. The duration of active labour before the start of the investigation was 3–46 h. In six patients the stomach was completely free of barium within 2–4.5 h. In four others there remained a slight trace of barium ("mucosal pattern") at 2 h (two patients), 4 h and 4.5 h, respectively. In the normal non-pregnant subject the barium is virtually emptied from the stomach within approximately 4 h.

Emptying was delayed in two patients. One had been in labour for 6 h, and barium remained in her stomach 6 h after the meal. The other had been in labour for 40 h and had incoordinate uterine activity. An appreciable quantity of intragastric barium remained at 8 h, and immediately before

Caesarean section, 26 h after the meal, there was a faint "mucosal pattern" of barium in the stomach.

Thus 10 of the 12 patients exhibited normal gastric emptying of semi-solid material during active labour. Only one had prolonged emptying time, with no obvious cause; unfortunately I have no record as to whether or not she, or any of the others, had received opioid analgesia.

On the basis of these direct observations, obtained in a study which is unlikely to be repeated, I suggest that only infrequently is gastric emptying time delayed during labour.

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NEUROMUSCULAR BLOCKERS BEFORE THIOPENTONE

Sir,—I was interested to read of the negative findings in the article by Levack and Spence [1], since I have been firmly convinced, from experience, that giving tubocurarine before thiopentone results in more favourable intubating conditions with minimum doses of both drugs. Atracurium and alcuronium appear to behave similarly. This is a very common belief among experienced anaesthetists and the reason put forward for the difference is that both drug actions peak together. I would suggest that, in addition, the redistribution of cardiac output that occurs with unconsciousness, as a result of reduction of normal vasoconstrictor tone in the skin blood vessels, results in slightly less of an administered drug going subsequently to the muscles. It would be of interest to know the effect of 50% nitrous oxide, which they used, on skin blood flow, as this might divert some neuromuscular blocker from the muscles in the same way.

The writers took care to point out that the end point they sought was a 90% depression in T1, and not the earliest onset of intubation conditions. The degree of muscle paralysis is related to the frequency of impulses arriving at the muscle, which depends on inactivation of the central nervous system in addition to depression of the end-plate. While 90% depression in T1 was awaited, the depth of anaesthesia may have waned. A further source of error could be the late arrival of drugs in the wrist where T1 depression was estimated, compared with the area of interest in the neck.

I still feel that there is a worthwhile advantage to be gained by injecting the neuromuscular blocker first *in selected cases*, but recommend it only if the patient has two "good" veins and the anaesthetist has two syringes of thiopentone prepared.

C. J. F. POTTER
Hythe

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HAEMODYNAMIC EFFECTS OF PROPOFOL

Sir,—The study by Claeys and his colleagues [1] on the haemodynamic effects of propofol anaesthesia showed that hypotension was a prominent feature of the use of this agent, and that this pressure decrease was caused by peripheral vasodilatation. In some circumstances deliberately induced hypotension is a feature of anaesthesia, and propofol could have a place in such techniques, perhaps permitting the dose of vasodilator agents such as nitroprusside to be reduced. In particular, the use of propofol might confer an advantage since, despite the occurrence of systemic hypotension, this was unaccompanied by pulmonary arterial hypotension. Pulmonary arterial hypotension and attendant impairment of gas exchange is a common feature of the use of vasodilators such as sodium nitroprusside and, to a lesser extent, nitroglycerin, in normal patients [2].

Unfortunately, data on arterial oxygenation are not given in the paper by Claeys [1], despite the sampling of arterial blood and reporting of other values from analysis of these samples. It is difficult to understand why oxygen tension values were not considered to be important, since the authors commented on moderate respiratory impairment. Such data would be of interest on clinical grounds alone, since the mean age of the patients was 62 yr, some were ASA III, and they breathed air during anaesthesia.

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Sir,—The results of our study revealed arterial hypotension mainly as result of decreased systemic vascular resistance (SVR), without a compensatory increase in heart rate or cardiac output. No pulmonary arterial hypotension was observed and Pa_{O_2} remained unchanged (Pa_{O_2} before propofol: 10.59 ± 1.8 kPa; Pa_{O_2} at 45 min: 9.78 ± 1.77 kPa (mean ± SEM)). The hypotensive effect of propofol disappeared rapidly after cessation of the propofol infusion. In our study all patients breathed room air spontaneously, and the measurements were obtained in the absence of surgical stimulation. However, other investigations have demonstrated an increase in SVR and systemic arterial pressure during surgery, although anaesthesia was deepened with 67% nitrous oxide [1, 2] or with fentanyl 10 $\mu g\ kg^{-1}$ [3]. A further increase in SVR when comparing controlled with spontaneous ventilation has also been observed [1, 2]. Since the decrease in SVR may be counteracted during positive pressure ventilation or by sympathetic reflex responses during surgery, the value of propofol for controlled hypotensive techniques might be questionable.

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SUXAMETHONIUM-SENSITIVE GENOTYPES

Sir,—I read with interest the report in your journal from Whittaker and Britten in which they analysed the results obtained by the Cholinesterase Research Unit during the first 2.5 years following its transfer from Exeter to London [1]. However, their conclusion that almost 25% of referrals have an $E_1^uE_1^s$ genotype (103 out of 430) is utterly beyond belief. $E_1^uE_1^s$ can be ascribed to patients only following family studies in which either parents or children are shown to be $E_1^sE_1^s$, $E_1^aE_1^s$ or $E_1^fE_1^s$. It is rare that this situation occurs.

Whittaker and Britten suggest that, for each patient found to be $E_1^uE_1^a$, there are five who are $E_1^uE_1^s$. The sensitivity to suxamethonium of these two genotypes would be expected to be similar and, accordingly, the frequency with which they present to a cholinesterase unit should reflect their occurrence in the general population. The incidence of $E_1^uE_1^a$ in this country approximates to 1 in 25 [2]; if Whittaker and Britten are to be believed, that of $E_1^uE_1^s$ will be 1 in 5 and, consequently, that of $E_1^sE_1^s$ 1 in 100. Since the observed incidence of $E_1^sE_1^s$ is less than 1 in 100000 [2], such a proposition is plainly absurd.

I suspect that the authors of this article have attributed an $E_1^uE_1^s$ genotype to everyone with enzyme inhibitor numbers characteristic of the usual phenotype, but who have a low cholinesterase activity. If this is so they are seriously mistaken. In a hospital population most such patients are $E_1^uE_1^u$, with a reduced cholinesterase activity secondary to their illness. Some are $E_1^uE_1^k$ or $E_1^uE_1^j$, while only a small proportion are $E_1^uE_1^s$.

If the reports of the Cholinesterase Research Unit are to be taken seriously, great care is required in the interpretation of their laboratory findings. Arbitrary ascription of a genotype such as $E_1^uE_1^s$ without supportive evidence from family studies will result in incorrect advice being given to patients. Some will be labelled "suxamethonium sensitive" when they are not, causing them unnecessary worry which subsequently will be difficult to allay. In addition, such a policy risks engendering doubt in the minds of professional colleagues as to the validity of other aspects of the work of the Cholinesterase Research Unit.

R. T. Evans
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Sir,—Dr Evans is quite right to focus attention on the high proportion of $E_1^uE_1^s$ individuals in our recent survey of suxamethonium-sensitive patients. Our classification of this group as genotypes is incorrect, since it must include several $E_1{}^u{}_1{}^k$, $E_1^kE_1^k$, $E_1^uE_1^j$, $E_1^jE_1^j$, $E_1^kE_1^s$ and $E_1^jE_1^s$ genotypes. None of these can be identified by inhibition studies, and even family evidence is often inconclusive. It would certainly have been desirable to label this group $E_1^uE_1^s$ phenotypes, although the segregation of the silent gene has been proven by family studies in more than 30% of this group of patients.

Segregation of the E_1^s allele is not easy to recognize, except in the homozygote with little or no enzymic activity. It is our belief that the incidence of the E_1^s gene in the British population is greater than that quoted by Dr Evans. This was calculated in the 1960s for a Caucasian population. From 1959 to 1970 we had only one $E_1^sE_1^s$ in our referrals and yet, during the past year, we have had six and eight silent homozygotes in London and Exeter, respectively. Furthermore we have had, during this period, an additional eight propositi who have been shown by family studies to have a probable $E_1^kE_1^s$ genotype. The frequency of the E_1^s allele has been reported to be very high in some of the higher castes in India and certainly varies in different ethnic groups. Our surprisingly high incidence of the $E_1^uE_1^s$ phenotype may be a reflection of the impact of the changing British population because of post-war immigration.

Until comparatively recently it was our policy to request a repeat sample from all individuals having a low cholinesterase activity and to query pregnancy, pathological or iatrogenic cause of the diminished activity. To resolve this uncertainty was the purpose of the request in our paper for details of the patient's diagnosis when the initial referral is made. When issuing a sensitivity card, one must be mindful of the clinical situation and assess the probability of a patient having a similar result with another anaesthetist on a subsequent occasion. It is difficult to deny from biochemical evidence that an incidence worthy of note has not occurred, in the absence of any reported abnormalities of technique. In borderline cases, we believe it is our duty to alert the patient that they will probably be moderately sensitive to suxamethonium.

M. Whittaker
Exeter
J. J. Britten
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FLOW REQUIREMENTS AND REBREATHING DURING MECHANICALLY CONTROLLED VENTILATION IN A T-PIECE (MAPLESON E)

Sir,—I question some of the advice offered to clinical anaesthetists by Drs Hatch, Yates and Lindahl [1].

Many combinations of fresh gas flow and minute ventilation can be used to achieve normocapnia using the T-piece and allied systems [2]. Rose and Froese [3] advocated low fresh gas flows which permit some alveolar rebreathing, and a minute ventilation more than sufficient to ensure near maximum fresh gas utilization. Small changes in minute volume then have negligible effects upon Pa_{CO_2} and continuous measurement of minute ventilation is relatively unimportant. Using a T-piece with a Nuffield 200 ventilator fitted with a Newton Valve [4], Hatch, Yates and Lindahl advised fresh gas flows high enough to avoid significant alveolar rebreathing. Under these circumstances, small changes in ventilation alter Pa_{CO_2} so that accurate control of minute ventilation becomes essential.

Most clinical anaesthetists lack the means to monitor the expired volume of small children continuously, and it would be hazardous to infer that a mean airway pressure of 1.8 kPa is a safe guide to an adequate tidal volume using a time-cycled pressure generator.

The statement that it is wise to monitor end-tidal carbon dioxide in children weighing less than 10 kg is welcome, but may I respectfully suggest that ideally it should be monitored in all children undergoing mechanical ventilation with a T-piece. In the meantime, those of us who still lack end-tidal carbon dioxide monitors may be advised to adhere to the recommendations of Rose and Froese [3].

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Sir,—Dr Morgan-Hughes is correct in stating that many combinations of fresh gas flow and minute ventilation can be used during controlled ventilation with the T-piece, although there have been few recommendations for children weighing less than 10 kg. The fresh gas flows suggested in our article are lower than the minimum of 3 litre min^{-1} advocated by Froese and Rose in 1982 [1]. These low fresh gas flows did not avoid significant alveolar rebreathing, but were found to permit normocapnia in infants with normal lungs ventilated adequately (ventilatory volumes previously set to give an end-tidal carbon dioxide tension (PE_{CO_2}) of 4.5 kPa under non-rebreathing conditions). It is true that our recommendations are higher than those of Froese and Rose for children heavier than 10 kg, since we found that their recommended flow of 3 litre min^{-1} caused an increase in PE_{CO_2} unless accompanied by a considerably increased minute volume. Dr Morgan-Hughes is not correct in stating that, under these circumstances, small changes in ventilation alter PCO_2, since the amount of rebreathing alters in parallel with changes in minute volume. One of the great advantages of this system, as he points out, is that PCO_2 stays relatively constant despite quite wide variations in ventilatory settings, a fact which can be shown in practice and in theory, both for the fresh gas flows recommended in our paper and those suggested by Froese and Rose.

We agree that it would be hazardous to infer that an airway pressure of 1.8 kPa indicated adequate ventilation. Indeed, when using the Newton Valve, airway pressure does not increase much above this value even if the tracheal tube becomes obstructed completely. However, we found it reassuring to note that this pressure, produced by adequate ventilation in our study, was comparable to pressures found in clinical practice. We agree also that, ideally, PE_{CO_2} should be measured, not only in children, but in all anaesthetized patients. This measurement becomes more important, however, in children of less than 10 kg weight in whom fresh gas flows of less than 3 litre min^{-1} are used.

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Br. J. Anaesth. (1988), **60**, 868–869

BOOK REVIEWS

Manual of Anesthesia in Cancer Care. By W. S. Howland, S. M. Rooney and P. L. Goldiner. Published by Churchill Livingstone. Pp. 321; indexed; illustrated. Price £22.00.

The concept of concentrating cancer care in one unit such as the Sloan Kettering Centre in New York is unfamiliar to many anaesthetists, who are accustomed to treating patients with cancer on routine operating sessions of individual surgical specialties. These anaesthetists become expert in problems peculiar to each individual specialty, but perhaps lack a general appreciation of the contribution of anaesthesia to cancer care. It was therefore anticipated that the accumulated wisdom of many years' experience of handling all aspects of cancer care would give insight into the problems, and practical guidance in the management of complex or unusual situations. In the preface the author comments that "attitudes about cancer by anaesthesiologists are often pessimistic or nihilistic" and express a desire to improve their understanding of management regimens and the possibilities for cure. Whilst applauding the author's motives, one cannot be but pessimistic regarding the outcome.

The book resembles a patchwork quilt in which materials of differing shapes and textures have been stitched together in a random manner. Despite the title the major portion of the text is devoted to non-anaesthetic topics, some of which are expanded to a degree inconsistent with their importance in the anaesthetic management of the patient. As an example, seven pages of the text are devoted to A.I.D.S. precautions, including guidelines on the labelling of specimen containers, whilst tracheotomy is allocated two pages, with no mention of the importance of tracheal toilet, methods of humidification, types of tracheostomy tube or cuff inflation pressures.

In many areas of the text it is difficult to determine the status of the anaesthetists to whom the book is addressed; at times, it is difficult to believe that the intended audience comprises anaesthetists. In contrast, the discussion of pulmonary flow catheters and the use of mass spectrometry in intra-operative monitoring implies the need for a degree of clinical expertise and knowledge of which many would be envious, yet the comment in complications of chemotherapy "if prolonged apnoea occurs after succinylcholine in patients who have been receiving cyclophosphamide, ventilatory support must be maintained", suggests an elementary level of comprehension.

A major criticism of the book is that it is not a manual, that is, a handy practical guide. The discursive nature of the text, a mixture of reviews of the literature, with hundreds of references, and anecdotal accounts of personal practice at Sloan Kettering, left this reader with a feeling of frustration. This was even more so in attempting to assess the practical treatment of a clinical problem.

The author's personal experience extending over 20 years in a major head and neck cancer surgical practice suggested he should analyse Case No. 9. Thiopentone and suxamethonium were given for induction and intubation, which was difficult because of associated trismus. The comment in the discussion is "of essence is airway control: if intubation is selected to maintain the airway, every effort should be made to accomplish this with the patient breathing. This may require topical anaesthetic agents, translaryngeal block or bilateral external laryngeal block." One can only concur, but where is the description of these techniques?—a reference to *Anesthesia and Analgesia*! There is no mention of the mechanical aids to the difficult intubation, for example, fibreoptic laryngoscopy, and most unfortunately no emphasis is placed on the importance of assessment of the airway before operation. The rule "if you think the patient needs a tracheostomy, he probably should have a tracheostomy" is unlikely to be helpful to the inexperienced physician searching for criteria on which to base a decision.

The advice that tracheostomy tubes should not be changed for 5 days is antiquated. Again, personal experience has shown that the use of a Bjork flap permits easy and safe changing of tubes within hours; the presence of the flap also preserves patency of the airway if the tube is misplaced accidentally and no postoperative stenosis has occurred. Contrary to a statement made, I believe that postoperative hypothermia and vasoconstriction is highly significant, and that the success of free flap reconstructions depends on adequate blood flow through microvascular anastomoses.

This book promised much, but failed to live up to expectations. Unfortunately, it cannot be seen as the definitive text on anaesthesia in cancer care, even if such a text is desirable.

R. S. Neill

Consciousness, Awareness and Pain in General Anaesthesia. Edited by M. Rosen and J. N. Lunn. Published by Butterworths, London. Pp. 195; illustrated; indexed; Price £29.50.

Consciousness is the most complex process in the universe and much of the literature concerning it has a certain philosophical woolliness, but if we are to tackle the relevant anaesthetic problems we have "to learn and to teach, not from the positions of philosophers, but from the fabric of nature". The merit of this international symposium is that, by and large, it does just that. There are a few injudicious statements by authors who appear not to have noted the facts reported in other chapters but, in the main, the accounts are factual and the conclusions suitably guarded.

Anaesthesia attenuates consciousness to many different planes and recent work suggests that it is seldom, if ever, completely obliterated. The only conclusive, direct, information we have comes from verbal communication with patients during anaesthesia; this was undertaken extensively during major surgery under light ether by Artusio, whose work gets due attention. Ether has gone into honourable retirement, so it is a pity that a similar study by the Bremen group (Barth and Büchel, 1975) is not mentioned. This monumental work was on nitrous oxide, the main agent for the majority of major surgery; moreover this study included nearly 800 patients, so that it is one of the few which yields statistically compelling results. I would also have liked a summary of John Snow's work in this field. Accurate observations and conclusive experiments are valid for all time; they are invaluable for the light they shed and as a model for others.

If verbal communication is seldom a practical method in routine work, it remains, nevertheless, the final yardstick for evaluating other, indirect, ways of measuring anaesthetic depth. The two main indirect methods are those which depend on physical signs, including the EMG, and those derived from the EEG. The data reported here show physical signs to have a rather poor correlation with conscious level, no doubt because they reflect mainly spinal cord and brainstem function, whilst consciousness is generated at higher levels. The relative dominance between brain and spinal cord varies from one individual to another, in common with all biological systems.

Consequently the EEG, which is closer to the relevant site, has attracted much attention in the past 30 years. The Northwick Park group showed that early evoked potentials (from the brainstem) correlate badly with anaesthetic depth, but the later ones (from the cortex) correlate well. Similarly, the Bonn team described a parameter which indentifies transition from consciousness to loss of verbal contact, namely the median frequency of the cortical EEG after Fourier analysis. Thus both teams are to be congratulated on making the EEG look potentially useful, at long last.

There are three chapters on a new stratum of consciousness identified by techniques of experimental psychology. The patient is unconscious in the sense of being unresponsive to verbal contact, but capable of retaining verbal information, especially emotive words relating to his prognosis. There is evidence that recovery is influenced favourably, or unfavourably, according to the information imparted. Clearly, this has important implications for everyday anaesthesia.

The anaesthetist who hitherto thought there was no awareness problem will be wiser after reading this book. Hopefully he will not over-react; undue concern on awareness has caused disasters from overdosage in recent years. It would be deplorable if this book increased the number of such disasters but, on balance, I think it will not. The main message from the last chapter and elsewhere is that, provided an established, thoroughly tested method is used, the risk of awareness, if not zero, is very small. Serious cases result from gross technical errors, such as failure of the nitrous oxide supply, but anyone who is scrupulous in avoiding these need have no fear.

There are four useful chapters by lawyers, who recognize the statistical nature of the problem. In court the anaesthetist is likely to lose his case if, for example, he used a technique for Caesarean section which is known to have a 2–5% failure rate. If, on the other hand, the method was one with a known failure rate of 1 in 500, then he is likely to be exonerated. No calculation is needed to see that evidence based on samples of 100 or less is almost worthless in this context. It seems regrettable, therefore, that no mention is made of the Glasgow studies comparing the failure rate of the main obstetric GA methods; these are unique in that the sample sizes ran into thousands.

In a slim volume errors of omission are inevitable; benzodiazepines, for example, deserve more attention than they get here. Enough carping; this is a valuable book. The printing has the Rolls-Royce quality we expect from Butterworths. I loved this sentence: "Who or what sort of thing is in there, looking at these extraordinarily complex displays of sensory information, sorting through the vast input, rejecting most items, storing others, or bringing them to the highest level (consciousness) and finally pulling the levers of response?" Don't we all wonder about this, between cases?

R. S. Cormack

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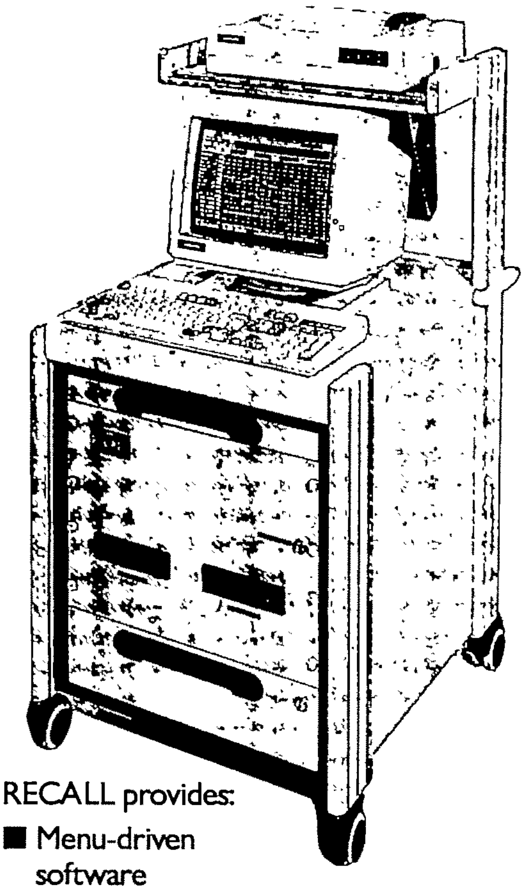

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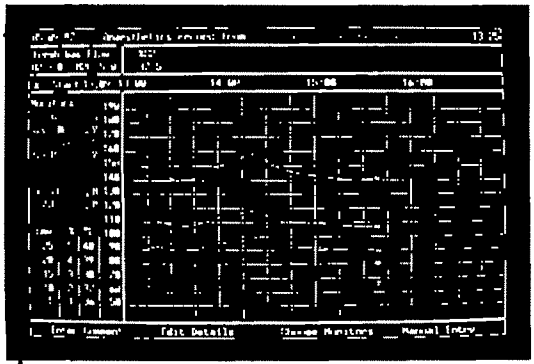

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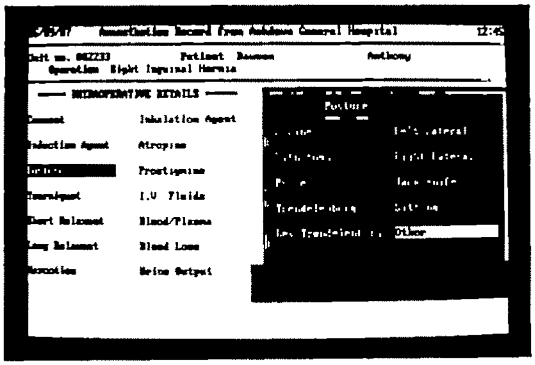

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